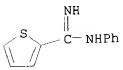
=> d l1

L1 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS
RN **3737-39-1** REGISTRY
CN 2-Thiophenecarboximidamide, N-phenyl- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 2-Thiophenecarboxamidine, N-phenyl- (6CI, 7CI, 8CI)
OTHER NAMES:
CN AR-R 16444
CN LTA
FS 3D CONCORD
MF C11 H10 N2 S
CI COM
LC STN Files: BEILSTEIN*, CA, CAOLD, CAPLUS, CASREACT, PHAR, TOXCENTER, USPATFULL
(*File contains numerically searchable property data)

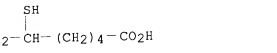


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

15 REFERENCES IN FILE CA (1962 TO DATE)
15 REFERENCES IN FILE CAPLUS (1962 TO DATE)
14 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

=> d l3

L3 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS
RN 462-20-4 REGISTRY
CN Octanoic acid, 6,8-dimercapto- (8CI, 9CI) (CA INDEX NAME)
OTHER NAMES:
CN (.+-.)-Dihydrolipoic acid
CN .alpha.-Lipoic acid, dihydro-
CN 6,8-Dihydrothioctic acid
CN 6,8-Dimercaptooctanoic acid
CN 6,8-Dithiooctanoic acid
CN Dihydrolipoic acid
CN Dihydrothioctic acid
CN DL-Dihydro-.alpha.-lipoic acid
CN dl-Dihydrolipoic acid
CN Reduced lipoic acid
CN Reduced thioctic acid
CN Thioctic acid, dihydro-
FS 3D CONCORD
DR **7516-48-5**
MF C8 H16 O2 S2
CI COM
LC STN Files: AGRICOLA, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CHEMCATS, CSCHEM, DDFU, DRUGU, EMBASE, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, RTECS*, TOXCENTER, USPAT2, USPATFULL
(*File contains numerically searchable property data)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

505 REFERENCES IN FILE CA (1962 TO DATE)
32 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
505 REFERENCES IN FILE CAPLUS (1962 TO DATE)
10 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

=> d his full

FILE 'REGISTRY' ENTERED AT 11:08:37 ON 11 MAR 2003
L1 1 SEA ABB=ON 3737-39-1/RN — compd A - see next pages
L2 2 SEA ABB=ON 3737-39-1/CRN " " in combn. " "
L3 1 SEA ABB=ON 7516-48-5/RN — compd. B —
L4 0 SEA ABB=ON L1 AND L3

FILE 'HCAPLUS' ENTERED AT 11:09:37 ON 11 MAR 2003
L5 23 SEA ABB=ON (L1 OR PHENYL?(W)2(W)?THIOPHENECARBOXIMID? OR ?PHENYL2THIOPHENECARBOXIMID?) 23 cits for Compd A
L6 3038 SEA ABB=ON (L3 OR ?LIPOIC?(W)?ACID? OR ?OCTANOIC?(W)?ACID?(3A)(?DIMERCAPTO? OR DI(W)?MERCAPTO?) 3038 cits for Compd B
L7 1 SEA ABB=ON L5 AND L6 1 cit for A+B — inventor - see pink tag yellow
L8 3060 SEA ABB=ON L5 OR L6 3060 cits for A or B

FILE 'REGISTRY' ENTERED AT 11:13:24 ON 11 MAR 2003
L9 1 SEA ABB=ON MPTP/CN

FILE 'HCAPLUS' ENTERED AT 11:14:06 ON 11 MAR 2003
L10 2 SEA ABB=ON L8 AND (L9 OR ?MPTP?)

FILE 'REGISTRY' ENTERED AT 11:15:01 ON 11 MAR 2003
E DOPAMINE/CN
L11 1 SEA ABB=ON DOPAMINE/CN

FILE 'HCAPLUS' ENTERED AT 11:15:30 ON 11 MAR 2003
L12 53 SEA ABB=ON L8 AND (L11 OR ?DOPAMIN? OR ?METABOL?(W)?ANTIOXID? OR ?SYNTHAS?(W)?INHIBIT?)
L13 28 SEA ABB=ON L12 AND (?FALL? OR ?REDUC? OR ?MINIMIZ? OR ?LESS? OR ?DROP?) (*)
L14 29 SEA ABB=ON L10 OR L13 29 cits for A or B combined with text terms

FILE 'CAOLD' ENTERED AT 11:20:11 ON 11 MAR 2003
L15 14 SEA ABB=ON (L1 OR PHENYL?(W)2(W)?THIOPHENECARBOXIMID? OR ?PHENYL2THIOPHENECARBOXIMID?) 14 cits in CA Old for Compd A

FILE 'CAOLD' ENTERED AT 11:22:44 ON 11 MAR 2003
L17 0 SEA ABB=ON L5 AND L6 0 cits in CA Old for A+B

FILE 'MEDLINE, BIOSIS, EMBASE, WPIDS, JICST-EPLUS, JAPIO' ENTERED AT 11:23:55 ON 11 MAR 2003
L18 24 SEA ABB=ON L5
L19 17 DUP REMOV L18 (7 DUPLICATES REMOVED) 17 cits in "other db's" for Compd A
L20 0 SEA ABB=ON L7 0 cits in "other db's" for A+B
L21 55 SEA ABB=ON L14
L22 40 DUP REMOV L21 (15 DUPLICATES REMOVED) 40 cits in "other databases" for A or B combined with text terms (*)

(*) Probably too broad to be useful, but included them anyway!

```
=> d que stat l15
L1             1 SEA FILE=REGISTRY ABB=ON  3737-39-1/RN
L15           14 SEA FILE=CAOLD ABB=ON  (L1 OR PHENYL?(W)2(W)?THIOPHENECARBOXIMI
                 D? OR ?PHENYL2THIOPHENECARBOXIMID?)

=> d ibib l15 1-14

L15  ANSWER 1 OF 14  CAOLD  COPYRIGHT 2003 ACS
ACCESSION NUMBER:  CA61:13613e  CAOLD
TITLE:             comparative study of the effect of radiation epilation in
                   mice treated before irradiation with cysteamine and
                   N-phenylamidines of pyromucic and 2-thiophenecarboxylic
                   acids
AUTHOR NAME:       Kaneti, Ya.; Robev, S.

L15  ANSWER 2 OF 14  CAOLD  COPYRIGHT 2003 ACS
ACCESSION NUMBER:  CA61:10981d  CAOLD
TITLE:             influence of N-phenylbenzamidine, N-phenyl-2-furamidine, and
                   N-phenylamidine of thiophene-2-carboxylic acid on the
                   radiation resistance of suspension of Bacillus anthracis, B.
                   cercus, Candida albicans, and Staphylococcus aureus in
                   irradiation with .gamma.-rays
AUTHOR NAME:       Robev, Stefan; Todorov, S.

L15  ANSWER 3 OF 14  CAOLD  COPYRIGHT 2003 ACS
ACCESSION NUMBER:  CA57:7573i  CAOLD
TITLE:             distribution of life spans in biol. collections-evaluating
                   studies in the course of the life span of biol. collections
                   as influenced by irradiation or administration of drugs
AUTHOR NAME:       Sippel, Arnulf; Heim, E.

L15  ANSWER 4 OF 14  CAOLD  COPYRIGHT 2003 ACS
ACCESSION NUMBER:  CA57:4990e  CAOLD
TITLE:             radioprotective effects of certain amidines on rats
                   preliminarily treated with zymosan
AUTHOR NAME:       Nikolov, Ivan

L15  ANSWER 5 OF 14  CAOLD  COPYRIGHT 2003 ACS
ACCESSION NUMBER:  CA57:2546g  CAOLD
TITLE:             kinetics of primary reactions and chem. protection
AUTHOR NAME:       Tarusov, B. N.

L15  ANSWER 6 OF 14  CAOLD  COPYRIGHT 2003 ACS
ACCESSION NUMBER:  CA57:1232a  CAOLD
TITLE:             combined radioprotective effect of radioprotectors of the
                   cysteamine and amidine series in rats irradiated by a lethal
                   dose of x-rays
AUTHOR NAME:       Nikolov, Ivan; Baev, I.

L15  ANSWER 7 OF 14  CAOLD  COPYRIGHT 2003 ACS
ACCESSION NUMBER:  CA56:7664a  CAOLD
TITLE:             radioprotective effect of the N-phenylamidine of
                   thiophenecarboxylic acid depending on the dose used
AUTHOR NAME:       Nikolov, Ivan; Baev, I.; Robev, S.

L15  ANSWER 8 OF 14  CAOLD  COPYRIGHT 2003 ACS
ACCESSION NUMBER:  CA55:23817g  CAOLD
TITLE:             radiation-protective action of N-phenylamidines of
```

2-thiophenecarboxylic acid and pyromucic acid
AUTHOR NAME: Baev, I.; Robev, S.

L15 ANSWER 9 OF 14 CAOLD COPYRIGHT 2003 ACS
ACCESSION NUMBER: CA55:20209b CAOLD
TITLE: summary of trials of various means of protection against acute radiation sickness
AUTHOR NAME: Rogozkin, V. D.

L15 ANSWER 10 OF 14 CAOLD COPYRIGHT 2003 ACS
ACCESSION NUMBER: CA55:693i CAOLD
TITLE: nuclear studies in bacteria
AUTHOR NAME: Chance, H. L.

L15 ANSWER 11 OF 14 CAOLD COPYRIGHT 2003 ACS
ACCESSION NUMBER: CA54:19841a CAOLD
TITLE: formation of glucosaminic acid by Acetobacter melanogenum and Pseudomonas fluorescens
AUTHOR NAME: Takahashi, Takeshi; Kayamori, H.

L15 ANSWER 12 OF 14 CAOLD COPYRIGHT 2003 ACS
ACCESSION NUMBER: CA53:22206i CAOLD
TITLE: protective effect of N-phenyl-substituted amidine of C6H6-, furan-, and thiophene series on the resistence of Escherichia coli suspension to irradiation of .gamma.-rays from Co60
AUTHOR NAME: Todorov, S.; Robev, S.

L15 ANSWER 13 OF 14 CAOLD COPYRIGHT 2003 ACS
ACCESSION NUMBER: CA52:20297g CAOLD
TITLE: effect of N-phenylamidine of thiophene-2-carboxylic acid on resistance of mice to irradiation with lethal doses of .gamma.-rays from Co60
AUTHOR NAME: Robev, Stephen

L15 ANSWER 14 OF 14 CAOLD COPYRIGHT 2003 ACS
ACCESSION NUMBER: CA52:18369h CAOLD
TITLE: rearrangement of the arylhydrazones of 2-thiophenealdehyde and of furfural into amidines
AUTHOR NAME: Robev, Stephen

Other Databases - for Compd A


```
=> d que stat 119
L1              1 SEA FILE=REGISTRY ABB=ON  3737-39-1/RN
L5             23 SEA FILE=HCAPLUS ABB=ON  (L1 OR PHENYL?(W)2(W)?THIOPHENECARBOXI
                  MID? OR ?PHENYL2THIOPHENECARBOXIMID?)
L18            24 SEA L5
L19            17 DUP REMOV L18 (7 DUPLICATES REMOVED)

=> d ibib abs l19 1-17

L19  ANSWER 1 OF 17  EMBASE  COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER:    2002448852  EMBASE
TITLE:               Novel inhibitors of neuronal nitric oxide synthase with
                     potent antioxidant properties.
AUTHOR:              Auvin S.; Auguet M.; Navet E.; Harnett J.J.; Viossat I.;
                     Schulz J.; Bigg D.; Chabrier P.-E.
CORPORATE SOURCE:    S. Auvin, Department of Medicinal Chemistry, Beaufour-Ipsen
                     Res. Laboratories, 5, Avenue du Canada, 91966 Les Ulis
                     Cedex, France. serge.auvin@beaufour-ipsen.com
SOURCE:              Bioorganic and Medicinal Chemistry Letters, (2003) 13/2
                     (209-212).
                     Refs: 12
                     ISSN: 0960-894X  CODEN: BMCLE8
PUBLISHER IDENT.:    S 0960-894X(02)00883-1
COUNTRY:             United Kingdom
DOCUMENT TYPE:       Journal; Article
FILE SEGMENT:        008     Neurology and Neurosurgery
                     037     Drug Literature Index
LANGUAGE:            English
SUMMARY LANGUAGE:    English
AB   A series of hybrid compounds possessing an nNOS pharmacophore linked to an
     antioxidant fragment has been synthesized. Among them, compound 8d, a
     propofol derivative, displayed the greatest dual potencies against nNOS
     (IC(50)=0.12 .mu.M) and lipid peroxidation (IC(50)=0.4 .mu.M) accompanied
     with e/nNOS selectivity (67.5). This shows that nNOS was able to
     accommodate very bulky groups such as di-tert-butyl or di-iso-propyl
     phenol in its active site. .COPYRGT. 2002 Elsevier Science Ltd. All rights
     reserved.

L19  ANSWER 2 OF 17  EMBASE  COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER:    2003073850  EMBASE
TITLE:               Oxidative stress in neurodegenerative diseases: Therapeutic
                     implications for superoxide dismutase mimetics.
AUTHOR:              Pong K.
CORPORATE SOURCE:    Dr. K. Pong, Department of Neuroscience, Wyeth Research,
                     Princeton, NJ 08543, United States. pongk@wyeth.com
SOURCE:              Expert Opinion on Biological Therapy, (2003) 3/1 (127-139).
                     Refs: 154
                     ISSN: 1471-2598  CODEN: EOBTA2
COUNTRY:             United Kingdom
DOCUMENT TYPE:       Journal; General Review
FILE SEGMENT:        005     General Pathology and Pathological Anatomy
                     008     Neurology and Neurosurgery
                     029     Clinical Biochemistry
                     037     Drug Literature Index
                     039     Pharmacy
LANGUAGE:            English
SUMMARY LANGUAGE:    English
AB   Evidence of oxidative stress is apparent in both acute and chronic
     neurodegenerative diseases, such as stroke, Parkinson's disease (PD) and
     amyotrophic lateral sclerosis (ALS). Increased generation of reactive
```

oxygen species simply overwhelm endogenous antioxidant defences, leading to subsequent oxidative damage and cell death. Tissue culture and animal models have been developed to mimic some of the biochemical changes and neuropathology found in these diseases. In doing so, it has been experimentally demonstrated that oxidative stress plays a critical role in neuronal cell death. Antioxidant enzymes, such as superoxide dismutase (SOD), catalase and glutathione peroxidase (GPx) have demonstrated therapeutic efficacy in models of neurodegeneration. However, delivery and stability issues have reduced the enthusiasm to clinically develop these proteins. Most recently, SOD mimetics, small molecules which mimic the activity of endogenous superoxide dismutase, have come to the forefront of antioxidant therapeutics. This review will examine the experimental evidence supporting the use of scavengers of superoxide anions in treating some neurodegenerative diseases, such as stroke, PD and ALS, but also the pitfalls that have met antioxidant molecules in clinical trials.

L19 ANSWER 3 OF 17 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2003047336 EMBASE
TITLE: Pharmacology of traumatic brain injury.
AUTHOR: Royo N.C.; Shimizu S.; Schouten J.W.; Stover J.F.; McIntosh T.K.
CORPORATE SOURCE: N.C. Royo, Head Injury Center, Department of Neurosurgery, University of Pennsylvania, 3320 Smith Walk, 105 C Hayden Hall, Philadelphia, PA 19104-6316, United States. nroyo@mail.med.upenn.edu
SOURCE: Current Opinion in Pharmacology, (2003) 3/1 (27-32). Refs: 74
ISSN: 1471-4892 CODEN: COPUBK
PUBLISHER IDENT.: S 1471-4892(02)00006-1
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 008 Neurology and Neurosurgery
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The intensity of experimental and clinical research to identify a neuroprotective drug for the treatment of traumatic brain injury is motivated by the devastating morbidity and mortality of this condition. Encouraging experimental work has led so fat to disappointing clinical trials and the identification of new potential therapeutic targets is critically dependent on a better understanding of the chronic pathophysiology triggered by the initial insult. Future advances in the pharmacological treatment of traumatic brain injury are likely to include the evaluation of sequentially timed therapies combining multiple and targeted agents, and manipulation of the newly discovered neurogenic potential of the adult brain together with the refinement of traditional interventions to block specific cytotoxic cascades.

L19 ANSWER 4 OF 17 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2003:43700 BIOSIS
DOCUMENT NUMBER: PREV200300043700
TITLE: N-(iminomethyl)amines derivatives, their preparation, their use as medicines and compositions containing them.
AUTHOR(S): Bigg, Dennis (1); Chabrier de Lassauniere, Pierre-Etienne; Auvin, Serge; Harnett, Jeremiah; Ulibarri, Gerard
CORPORATE SOURCE: (1) Gif-sur-Yvette, France France
ASSIGNEE: Societe de Conseils de Recherches et d'Applications Scientifiques (S.C.R.A.S.), France
PATENT INFORMATION: US 6482822 November 19, 2002

SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (Nov. 19 2002) Vol. 1264, No. 3, pp. No Pagination. http://www.uspto.gov/web/menu/patdata.html. e-file.
ISSN: 0098-1133.
DOCUMENT TYPE: Patent
LANGUAGE: English
AB The invention concerns novel N-(iminomethyl)amine derivatives comprising in their skeleton the aminophenylamine, oxodiphenylamine, carbazole, phenazine, phenoxazine or oxodiphenyl motif, their use as medicines and pharmaceutical compositions containing them. The invention concerns in particular the following compounds: -4-{[2-thienyl(imino)methyl]amino}-N-[2-(phenylamino)phenyl]-benzenebutana mide; -4-{[2-thienyl(imino)methyl]amino}-N-[4-(phenylamino)phenyl]-benzenebutana mide; -N-'[4-(10H-phenothiazin-2-yloxy)**phenyl**]-2-**thiophenecarboximidamide**; -4-(4-{[amino(2-thienyl)methylidene]amino}phenyl)-N-(10H-phenothiazin-3-yl H)butanamide; -3-[(3-{[amino(2-thienyl)methylidene]amino}-benzyl)amino]-N-(4-anilinophen yl)propanamide; -N'-(4-{2-[(10H-phenothiazin-3-ylmethyl)amino]ethyl}phenyl-2-thiophene carboximidamide.

L19 ANSWER 5 OF 17 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2002387764 EMBASE
TITLE: Synthesis and evaluation of 4-hydroxyphenylacetic acid amides and 4-hydroxycinnamamides as antioxidants.
AUTHOR: Jung Y.-S.; Kang T.-S.; Yoon J.-H.; Joe B.-Y.; Lim H.-J.; Seong C.-M.; Park W.-K.; Kong J.-Y.; Cho J.; Park N.-S.
CORPORATE SOURCE: N.-S. Park, Medicinal Science Division, Korea Res. Inst. of Chem. Technology, PO Box 107, Yusong, Taejon 305-606, Korea, Republic of. nspark@krict.re.kr
SOURCE: Bioorganic and Medicinal Chemistry Letters, (16 Sep 2002) 12/18 (2599-2602).
Refs: 16
ISSN: 0960-894X CODEN: BMCLE8
PUBLISHER IDENT.: S 0960-894X(02)00479-1
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 008 Neurology and Neurosurgery
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB 4-Hydroxyphenylacetic acid amides and 4-hydroxycinnamamides were synthesized and their antioxidant and neuroprotective activities were evaluated. Among the prepared compounds, 6f, 6g, 8b, and 9 exhibited potent inhibition of lipid peroxidation in rat brain homogenates, and marked DPPH radical scavenging activities. Furthermore, 6f, 6g, and 9 exhibited neuroprotective action against the oxidative damage induced by the exposure of primary cultured rat cortical cells to H(2)O(2), xanthine/xanthine oxidase, or Fe(2+)/ascorbic acid. Based on these results, we found that 6f was the most potent antioxidant among the compounds tested. .COPYRGT. 2002 Elsevier Science Ltd. All rights reserved.

L19 ANSWER 6 OF 17 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2002184667 EMBASE
TITLE: NXY-059. Treatment of ischemic stroke free, radical scavenger.
AUTHOR: Sorbera L.A.; Leeson P.A.; Castaner J.; Del Fresno M.
CORPORATE SOURCE: L.A. Sorbera, Prous Science, P.O. Box 540, 08080 Barcelona,

Spain
SOURCE: Drugs of the Future, (2002) 27/3 (240-247).
Refs: 22
ISSN: 0377-8282 CODEN: DRFUD4
COUNTRY: Spain
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Stroke is considered the third leading cause of death and the major cause of disability in the U.S. There are 2 major therapeutic options available for the treatment of stroke and they are targeting of the insufficient arterial oxygen and glucose resulting from stroke by enhancing blood flow and neuroprotection. One group of neuroprotective agents are the free radical scavengers and free radical production inhibitors; within this group the novel spin trap class of agents have emerged. NXY-059 is a spin trap agent that was designed to treat ischemic stroke but is not contraindicated in hemorrhagic stroke. NXY-059 has demonstrated considerable neuroprotective effects in preclinical studies and has been shown to be safe and effective in clinical trials involving patients with acute stroke.

L19 ANSWER 7 OF 17 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2002155494 EMBASE
TITLE: Nitric oxide related therapeutic phenomenon: A challenging task.
AUTHOR: Alcaraz M.J.; Guillen M.I.
CORPORATE SOURCE: M.J. Alcaraz, Department of Pharmacology, Faculty of Pharmacy, University of Valencia, Av. Vicent Andres Estelles s/n, 46100 Burjassot, Valencia, Spain. maria.j.alcaraz@uv.es
SOURCE: Current Pharmaceutical Design, (2002) 8/3 (215-231).
Refs: 243
ISSN: 1381-6128 CODEN: CPDEFP
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Nitric oxide (NO), produced from L-arginine by the activity of constitutive and inducible NO synthases, has been implicated in a wide range of physiological and pathophysiological processes. Low concentrations of this mediator play homeostatic roles, whereas NO is up-regulated in a number of pathological states and can have damaging effects. Pharmacological modulation of NO levels or NO biosynthesis may be a therapeutic strategy for a number of conditions, although the reported results can be some times controversial. Inhibitors of NO synthases exhibit different selectivity for the neuronal, endothelial or inducible isoforms, which contributes to their beneficial and detrimental effects. Recent developments in this field may offer an alternative for the treatment of inflammatory disorders, pain, neurological diseases, shock, atherosclerosis or cancer.

L19 ANSWER 8 OF 17 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2002155492 EMBASE
TITLE: Progress in the development of selective nitric oxide synthase (NOS) inhibitors.

AUTHOR: Salerno L.; Sorrenti V.; Di Giacomo C.; Romeo G.; Siracusa M.A.
CORPORATE SOURCE: L. Salerno, Dipartimento Scienze Farmaceutiche, Universita di Catania, Chimica Medica e Biologia Molecolare, Viale A. Doria 6, 95125 Catania, Italy. L.Salerno@mbox.unict.it
SOURCE: Current Pharmaceutical Design, (2002) 8/3 (177-200).
Refs: 147
ISSN: 1381-6128 CODEN: CPDEFP
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 008 Neurology and Neurosurgery
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Nitric oxide (NO), a molecular messenger synthesized by nitric oxide synthase (NOS) from L-arginine and molecular oxygen, is involved in a number of physiological and pathological processes in mammalians. Three structurally distinct isoforms of NOS have been identified: neuronal (nNOS), endothelial (eNOS) and inducible (iNOS). Although NO mediates several physiological functions, overproduction of NO by nNOS has been reported in a number of clinical disorders including acute (stroke) and chronic (schizophrenia, Alzheimer's, Parkinson's and AIDS dementia) neurodegenerative diseases, convulsions and pain; overproduction of NO by iNOS has been implicated in various pathological processes including septic shock, tissue damage following inflammation and rheumatoid arthritis. On the contrary, NO produced by eNOS has only physiological roles such as maintaining physiological vascular tone. Accordingly, selective inhibition of nNOS or iNOS vs eNOS may provide a novel therapeutic approach to various diseases; in addition selective inhibitors may represent useful tools for investigating other biological functions of NO. For these reasons, after the identification of N-methyl-L-arginine (L-NMA) as the first inhibitor of NO biosynthesis, design of selective NOS inhibitors has received much attention.

L19 ANSWER 9 OF 17 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2001348654 EMBASE
TITLE: Pharmacologic therapy in traumatic brain injury: Update on experimental treatment strategies.
AUTHOR: Laurer H.L.; McIntosh T.K.
CORPORATE SOURCE: T.K. McIntosh, Department of Neurosurgery, Univ. of Pennsylvania Medical School, Veterans Administration Medical Ctr., 3320 Smith Walk, 105 Hayden Hall, Philadelphia, PA 19104-6316, United States. mcintosh@seas.upenn.edu
SOURCE: Current Pharmaceutical Design, (2001) 7/15 (1505-1516).
Refs: 132
ISSN: 1381-6128 CODEN: CPDEFP
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 008 Neurology and Neurosurgery
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Considerable effort has led to an increased interest in emerging preclinical and clinical data regarding the pathophysiological changes in the posttraumatic brain. It is widely believed that delayed cell damage and death contributes to behavioral impairment following traumatic brain

injury. However, no drug therapy to attenuate this process is available at present, and the development of new therapeutic regimen is urgently warranted. This manuscript represents a compendium of recent preclinical work undertaken to evaluate new pharmacologic strategies in the experimental setting as a first step towards the development of a therapeutic armamentarium directed to improve functional recovery in head-injured patients.

L19 ANSWER 10 OF 17 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2002090604 EMBASE
TITLE: Pharmacology down under in 2001.
AUTHOR: Doggrell S.A.
CORPORATE SOURCE: Dr. S.A. Doggrell, Department of Physiology, School of Biomedical Sciences, University of Queensland, Brisbane, QLD 4072, Australia
SOURCE: Drug News and Perspectives, (2001) 14/10 (630-640).
Refs: 31
ISSN: 0214-0934 CODEN: DNPEED
COUNTRY: Spain
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 017 Public Health, Social Medicine and Epidemiology
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Every December, pharmacologists and toxicologists of Australia and New Zealand gather for the Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists annual scientific meeting. The 2001 meeting highlighted the areas of cardiovascular research and neurodegeneration and neuroprotection. Cardiovascular researchers are investigating such areas as drugs for pulmonary hypertension, links between superoxide dismutase and cardiovascular disease, and angiogenesis. There was considerable discussion as to why neuroprotective agents that are so promising in animals fail in the clinic. Potential new agents and new targets for neuroprotection were also considered. .COPYRGT. 2002 Prous Science. All rights reserved.

L19 ANSWER 11 OF 17 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2001050202 EMBASE
TITLE: The ischaemic penumbra.
AUTHOR: Touzani O.; Roussel S.; MacKenzie E.T.
CORPORATE SOURCE: O. Touzani, Boulevard H. Becquerel, 14074 Caen Cedex, France. o.touzani@cyceron.fr
SOURCE: Current Opinion in Neurology, (2001) 14/1 (83-88).
Refs: 75
ISSN: 1350-7540 CODEN: CONEEX
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 008 Neurology and Neurosurgery
014 Radiology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The concept of an ischaemic penumbra, surrounding a focal cerebral lesion, is now widely accepted, although no universal definition of the 'penumbra' exists. In the present review, we consider the penumbra as that volume of brain tissue at the periphery of a focal, irreversibly damaged area that is threatened by recruitment into necrosis. Implicit to such a definition are several secondary concepts. First, the penumbra is both spatial, in that it surrounds the densely ischaemic core, but it is also temporal, in

that its evolution toward infarction is a relatively progressive phenomenon. The pertinent literature is summarized. Second, penumbral tissue is potentially salvageable; the most recent animal studies are reviewed. Third, because electrically silent and pathologically damaged tissues have identical functional characteristics, it is evident that most clinical rating scales, be they neurological, behavioural, or psychological, are poorly adapted to address the problem of the penumbra. Finally, the penumbral tissue is remarkably and intensively 'active': Multiple processes of cell death and repair occur and involve molecular mechanisms, electrophysiology and the vasculature. .COPYRGT. 2001 Lippincott Williams & Wilkins.

L19 ANSWER 12 OF 17 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 2000421445 MEDLINE
DOCUMENT NUMBER: 20399633 PubMed ID: 10945536
TITLE: Radiolabeled neuronal nitric oxide synthase inhibitors: synthesis, in vivo evaluation, and primate PET studies.
AUTHOR: Pomper M G; Musachio J L; Scheffel U; Macdonald J E; McCarthy D J; Reif D W; Villemagne V L; Yokoi F; Dannals R F; Wong D F
CORPORATE SOURCE: Department of Radiology, Johns Hopkins University School of Medicine, Baltimore, Maryland 21287-2182, USA.
SOURCE: JOURNAL OF NUCLEAR MEDICINE, (2000 Aug) 41 (8) 1417-25. Journal code: 0217410. ISSN: 0161-5505.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200009
ENTRY DATE: Entered STN: 20000915
Last Updated on STN: 20000915
Entered Medline: 20000905

AB The objectives of this study were to synthesize neuronal nitric oxide synthase (NOS-I)-selective imaging agents based on the 2 potent, selective inhibitors AR-R 17443 [N-(4-((2-((phenylmethyl) (methyl)-amino)ethyl) **phenyl**)-**2-thiophenecarboximidamide**)] and AR-R 18512 [(N(2-methyl-1,2,3,4-tetrahydroisoquinoline-7-yl)-2-thiophenecarboxim idamide)] in positron-emitting form and to evaluate regional brain uptake in rodents and primates. METHODS: [11C]AR-R 17443 and [11C]AR-R 18512 were produced by N-alkylation of the corresponding desmethyl precursors using [11C]iodomethane. Regional brain uptake of [11C]AR-R 17443 and [11C]AR-R 18512 was assayed in rats and NOS-I knockout mice, and PET was performed in baboons. Tracer kinetic modeling used a 2-compartment plasma and brain tissue model. RESULTS: Yields of [11C]AR-R 17443 and [11C]AR-R 18512 ranged from 8% to 16% at the end of synthesis, with specific activities of 50-178 GBq/micromol (1,350-4,800 Ci/mmol) at the end of synthesis. In rat cerebellum and cortex at 30 min after injection, [11C]AR-R 17443 showed 1.01 +/- 0.01 and 1.63 +/- 0.12 percentage injected dose per gram (%ID/g) uptake, respectively, whereas [11C]AR-R 18512 showed 0.88 +/- 0.01 and 1.30 +/- 0.07 %ID/g uptake, respectively. Attempts to block tracer uptake by pretreatment with the NOS-I-selective inhibitor 7-nitroindazole or the corresponding unlabeled inhibitor (or desmethyl precursor to AR-R 17443 of similar potency) were unsuccessful. A small but significant (20%) decrease in cerebellar uptake of [11C]AR-R 18512 was present in NOS-I knockout mice compared with control mice. PET of [11C]AR-R 18512 in baboons with concurrent regional cerebral blood flow (rCBF) determination before and after administration of blocker showed dose-related decreases in cerebellar uptake that were greater than or equal to decreases in rCBF. Plasma metabolites accounted for 27% of total activity at 30 min after injection. Kinetic modeling of

binding potentials revealed a distribution volume of 334 in cerebral blood that dropped 51% after blocker administration. CONCLUSION: Rodent studies for [11C]AR-R 17443 and [11C]AR-R 18512 showed little evidence of specific NOS-I binding. In baboons, we detected a higher uptake of [11C]AR-R 18512 in the cerebellum than in the cortex (approximately 5%, accounting for decreased rCBF because of blockade), indicating minimal specific binding. Analogs of higher affinity are likely required if this class of agents is to prove viable for PET.

L19 ANSWER 13 OF 17 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2000172719 EMBASE
TITLE: BN 80933 inhibits F2-isoprostane elevation in focal cerebral ischaemia and hypoxic neuronal cultures.
AUTHOR: Marin J.-G.; Cornet S.; Spinnewyn B.; Demerle-Pallardy C.; Auguet M.; Chabrier P.-E.
CORPORATE SOURCE: P.-E. Chabrier, Beaufour-IPSEN Research Laboratories, Institut Henri Beaufour, 5 Avenue du Canada, 91966 Les Ulis Cedex, France
SOURCE: NeuroReport, (27 Apr 2000) 11/6 (1357-1360).
Refs: 24
ISSN: 0959-4965 CODEN: NERPEZ
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 008 Neurology and Neurosurgery
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Formation of the lipid peroxidation product 8-epi-prostaglandin2.alpha. (8- epi-PGF2.alpha.) a bioactive marker of oxidative stress, was quantified in in vitro and in vivo models of neuronal death. In culture media of primary rat cortical neurones exposed to hypoxia followed by reoxygenation, a 3.7-fold increase of 8-epi-PGF2.alpha. concentration was observed in comparison to control cells. In rats submitted to 2 h middle cerebral artery occlusion followed by a 22 h reperfusion period, a 27-fold increase of 8-epi-PGF2.alpha. was observed in the ischaemic hemisphere compared with the corresponding hemisphere of sham-operated rats. Treatment with the neuroprotective agent BN 80933 significantly reduced both 8-epi-PGF2.alpha. elevations in vitro and in vivo. These data suggest that 8-epi-PGF2.alpha. elevations might reflect the damaging free radical overproduction and subsequent lipid peroxidation during neuronal injury induced by hypoxia and ischaemia. Inhibition of 8-epi-PGF2.alpha. elevations participates to the neuroprotective effects of BN 80933. (C) 2000 Lippincott Williams and Wilkins.

L19 ANSWER 14 OF 17 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2001009740 EMBASE
TITLE: Acute stroke therapy: Translating preclinical neuroprotection to therapeutic reality.
AUTHOR: Parsons A.A.; Irving E.A.; Legos J.J.; Lenhard S.C.; Chandra S.; Schaeffer T.R.; Haimbach R.E.; White R.F.; Hunter A.J.; Barone F.C.
CORPORATE SOURCE: A.A. Parsons, SmithKline Beecham Pharmaceuticals, Neuroscience Research, New Frontiers Science Park, Third Avenue, Harlow, Essex CM19 5AW, United Kingdom. Andrew_A_Parsons@sbphrd.com
SOURCE: Current Opinion in Investigational Drugs, (2000) 1/4 (452-463).
Refs: 127
ISSN: 0967-8298 CODEN: CIDREE
COUNTRY: United Kingdom

DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 008 Neurology and Neurosurgery
037 Drug Literature Index
030 Pharmacology
014 Radiology
005 General Pathology and Pathological Anatomy
018 Cardiovascular Diseases and Cardiovascular Surgery
LANGUAGE: English

L19 ANSWER 15 OF 17 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 2
ACCESSION NUMBER: 2000:382757 BIOSIS
DOCUMENT NUMBER: PREV200000382757
TITLE: ARL 17477, a selective nitric oxide synthase inhibitor, with neuroprotective effects in animal models of global and focal cerebral ischaemia.
AUTHOR(S): O'Neill, Michael J. (1); Murray, Tracey K.; McCarty, Deborah R.; Hicks, Caroline A.; Dell, Colin P.; Patrick, Kelly E.; Ward, Mark A.; Osborne, David J.; Wiernicki, Todd R.; Roman, Carlos R.; Lodge, David; Fleisch, Jerome H.; Singh, JaiPal
CORPORATE SOURCE: (1) Lilly Research Centre, Eli Lilly and Co. Ltd., Erl Wood Manor, Windlesham, Surrey, GU20 6PH UK
SOURCE: Brain Research, (21 July) Vol. 871, No. 2, pp. 234-244. print.
ISSN: 0006-8993.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
AB In the present studies, we have evaluated the effects of N-(4-(2-(((3-Chlorophenyl)methyl)amino)ethyl)**phenyl**)-2**-thiophenecarboximidamide** dihydrochloride (ARL 17477) on recombinant human neuronal NOS (nNOS) and endothelial NOS (eNOS). We then carried out pharmacokinetic studies and measured cortical nitric oxide synthase (NOS) inhibition to determine that the compound crossed the blood brain barrier. Finally, the compound was evaluated in a model of global ischaemia in the gerbil and two models of transient focal ischaemia in the rat. The IC50 values for ARL 17477 on human recombinant human nNOS and eNOS were 1 and 17 muM, respectively. ARL 17477 (50 mg/kg i.p.) produced a significant reduction in the ischaemia-induced hippocampal damage following global ischaemia when administered immediately post-occlusion, but failed to protect when administration was delayed until 30 min post-occlusion. In the endothelin-1 model of focal ischaemia, ARL 17477 (1 mg/kg i.v.) significantly attenuated the infarct volume when administered at either 0, 1 or 2 h post-endothelin-1 ($P<0.05$). In the intraluminal suture model, ARL 17477 at both 1 and 3 mg/kg i.v. failed to reduce the infarct volume measured at 1, 3 or 7 days post-occlusion. These results demonstrate that ARL 17477 protects against global ischaemia in gerbils and provides some reduction in infarct volume following transient middle cerebral artery occlusion in rats, indicating that nNOS inhibition may be a useful treatment of ischaemic conditions.

L19 ANSWER 16 OF 17 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 1999415943 MEDLINE
DOCUMENT NUMBER: 99415943 PubMed ID: 10485910
TITLE: BN 80933, a dual inhibitor of neuronal nitric oxide synthase and lipid peroxidation: a promising neuroprotective strategy.
COMMENT: Comment in: Proc Natl Acad Sci U S A. 1999 Sep 14;96(19):10557-8

AUTHOR: Chabrier P E; Auguet M; Spinnewyn B; Auvin S; Cornet S; Demerle-Pallardy C; Guilmard-Favre C; Marin J G; Pignol B; Gillard-Roubert V; Roussillot-Charnet C; Schulz J; Viossat I; Bigg D; Moncada S
CORPORATE SOURCE: Beaufour-Ipsen Research Laboratories, Institut Henri Beaufour, 5 Avenue du Canada, 91966 Les Ulis Cedex, France.. pierreet.chabrier@beaufour-ipsen.com
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1999 Sep 14) 96 (19) 10824-9. Journal code: 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199910
ENTRY DATE: Entered STN: 19991026
Last Updated on STN: 19991026
Entered Medline: 19991014

AB Nitric oxide (NO) and reactive oxygen species (ROS) act independently as well as cooperatively to induce neuronal death in acute neurological disorders. Inhibition of neuronal nitric oxide synthase (nNOS) and inhibition of lipid peroxidation induced by ROS have both been proposed as neuroprotective strategies in stroke and trauma. Recently, in our laboratory, the combination of the two strategies was found to be synergistic in reducing neuronal damage. Here, we report that BN 80933 [(S)-N- 4-[4-[(3,4-dihydro-6-hydroxy-2, 5,7, 8-tetramethyl-2H-1-benzopyran-2-yl)carbonyl]-1-piperazinyl]**phenyl -2-thiophenecarboximidamide**], a compound that combines potent antioxidant and selective nNOS inhibitory properties in vitro, affords remarkable neuronal protection in vivo. Intravenous administration of BN 80933 significantly reduced brain damage induced by head trauma in mice, global ischemia in gerbils, and transient focal ischemia in rats. Treatment with BN 80933 (0.3-10 mg/kg) significantly reduced infarct volume (>60% protection) and enhanced behavioral recovery in rats subjected to transient (2-h) middle cerebral artery occlusion and 48-h or 7-day reperfusion. Furthermore, treatment with BN 80933 commencing up to 8 h after the onset of ischemia resulted in a significant improvement of neurological outcome. All these results indicate that BN 80933 represents a class of potentially useful therapeutic agents for the treatment of stroke or trauma and possibly neurodegenerative disorders that involve both NO and ROS.

L19 ANSWER 17 OF 17 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 2000021349 MEDLINE
DOCUMENT NUMBER: 20021349 PubMed ID: 10554878
TITLE: Synergistic neuroprotective effects by combining an NMDA or AMPA receptor antagonist with nitric oxide synthase inhibitors in global cerebral ischaemia.
AUTHOR: Hicks C A; Ward M A; Swettenham J B; O'Neill M J
CORPORATE SOURCE: Eli Lilly & Company, Lilly Research Centre, Windlesham, Surrey, UK.
SOURCE: EUROPEAN JOURNAL OF PHARMACOLOGY, (1999 Sep 24) 381 (2-3) 113-9. Journal code: 1254354. ISSN: 0014-2999.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199912
ENTRY DATE: Entered STN: 20000113

Last Updated on STN: 20000113
Entered Medline: 19991213

AB We have investigated the neuroprotective effects of combining an NMDA or AMPA receptor antagonist with a nitric oxide synthase (NOS) inhibitor in the gerbil model of global cerebral ischaemia. Ischaemia was induced by occlusion of the common carotid arteries for 5 min. (5R,10S)-(+)-5-methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,1 0-imine (MK-801, 2.5 mg/kg i.p.) or (3S,4aR,6R,8aR)-6-[2-(1(2)H-tetrazole-5-yl)]decahydroisoq uinoline-3-carboxylic acid (LY293558, 20 mg/kg i.p.) and 7-nitroindazole (25 mg/kg i.p.) or N-[4-(2-[[(3-chlorophenyl)methyl]amino]ethyl) **phenyl]-2-thiophenecarboximidamide** dihydrochloride (ARL17477, 25 mg/kg i.p.) were administered alone or in combination (i.e., MK-801 with 7-nitroindazole or ARL17477 or LY293558 with 7-nitroindazole or ARL17477). In the present studies, both MK-801 and LY293558 provided significant degree of neuroprotection, while 7-nitroindazole and ARL17477 also provided some neuroprotection, which failed to reach significance in every case. However, the combination of MK-801 with 7-nitroindazole or ARL17477 provided 21% or 44% greater protection than the total protection or either alone. Likewise, the combination of LY293558 with 7-nitroindazole or ARL17477 provided 14.5% and 35% greater protection than total protection of either compound alone. These results indicate that several pathways contribute to ischaemic cell death and combining excitatory amino antagonists and NOS inhibitors provides greater protection than either alone. Therefore, combination therapy should be considered as an approach for treating ischaemic conditions.

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 NEWS  3  Apr 09  BEILSTEIN: Reload and Implementation of a New Subject Area
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 NEWS  5  Apr 19  US Patent Applications available in IFICDB, IFIPAT, and IFIUDB
 NEWS  6  Apr 22  Records from IP.com available in CAPLUS, HCAPLUS, and ZCAPLUS
 NEWS  7  Apr 22  BIOSIS Gene Names now available in TOXCENTER
 NEWS  8  Apr 22  Federal Research in Progress (FEDRIP) now available
 NEWS  9  Jun 03  New e-mail delivery for search results now available
 NEWS 10  Jun 10  MEDLINE Reload
 NEWS 11  Jun 10  PCTFULL has been reloaded
 NEWS 12  Jul 02  FOREGE no longer contains STANDARDS file segment
 NEWS 13  Jul 22  USAN to be reloaded July 28, 2002;
                  saved answer sets no longer valid
 NEWS 14  Jul 29  Enhanced polymer searching in REGISTRY
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 NEWS 17  Aug 08  PHARMAMarketLetter(PHARMAML) - new on STN
 NEWS 18  Aug 08  NTIS has been reloaded and enhanced
 NEWS 19  Aug 19  Aquatic Toxicity Information Retrieval (AQUIRE)
                  now available on STN
 NEWS 20  Aug 19  IFIPAT, IFICDB, and IFIUDB have been reloaded
 NEWS 21  Aug 19  The MEDLINE file segment of TOXCENTER has been reloaded
 NEWS 22  Aug 26  Sequence searching in REGISTRY enhanced
 NEWS 23  Sep 03  JAPIO has been reloaded and enhanced
 NEWS 24  Sep 16  Experimental properties added to the REGISTRY file
 NEWS 25  Sep 16  CA Section Thesaurus available in CAPLUS and CA
 NEWS 26  Oct 01  CASREACT Enriched with Reactions from 1907 to 1985
 NEWS 27  Oct 21  EVENTLINE has been reloaded
 NEWS 28  Oct 24  BEILSTEIN adds new search fields
 NEWS 29  Oct 24  Nutraceuticals International (NUTRACEUT) now available on STN
 NEWS 30  Oct 25  MEDLINE SDI run of October 8, 2002
 NEWS 31  Nov 18  DKILIT has been renamed APOLLIT
 NEWS 32  Nov 25  More calculated properties added to REGISTRY
 NEWS 33  Dec 02  TIBKAT will be removed from STN
 NEWS 34  Dec 04  CSA files on STN
 NEWS 35  Dec 17  PCTFULL now covers WP/PCT Applications from 1978 to date
 NEWS 36  Dec 17  TOXCENTER enhanced with additional content
 NEWS 37  Dec 17  Adis Clinical Trials Insight now available on STN
 NEWS 38  Dec 30  ISMEC no longer available
 NEWS 39  Jan 13  Indexing added to some pre-1967 records in CA/CAPLUS
 NEWS 40  Jan 21  NUTRACEUT offering one free connect hour in February 2003
 NEWS 41  Jan 21  PHARMAML offering one free connect hour in February 2003
 NEWS 42  Jan 29  Simultaneous left and right truncation added to COMPENDEX,
                  ENERGY, INSPEC
 NEWS 43  Feb 13  CANCERLIT is no longer being updated
 NEWS 44  Feb 24  METADEX enhancements
 NEWS 45  Feb 24  PCTGEN now available on STN
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NEWS 46  Feb 24  TEMA now available on STN
NEWS 47  Feb 26  NTIS now allows simultaneous left and right truncation
NEWS 48  Feb 26  PCTFULL now contains images
NEWS 49  Mar 04  SDI PACKAGE for monthly delivery of multifile SDI results

NEWS EXPRESS  January 6 CURRENT WINDOWS VERSION IS V6.01a,
              CURRENT MACINTOSH VERSION IS V6.0b(ENG) AND V6.0Jb(JP),
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FILE 'MEDLINE' ENTERED AT 13:32:33 ON 12 MAR 2003

=> s N-phenyl-2-thiophenecarboximidamine
L1            1 N-PHENYL-2-THIOPHENECARBOXIMIDAMINE

=> d ab,bib

L1   ANSWER 1 OF 1  CA  COPYRIGHT 2003 ACS
AB   The invention relates to a pharmaceutical compn. comprising as an active
     ingredient one or several substances interfering with the synthesis of
     nitrogen monoxide by inhibiting NO-synthase and one or several metabolic
     antioxidants contg. thiol groups and intervening in the redox status of
     the thiol groups, and optionally a pharmaceutically acceptable support.
     The invention also relates to a product contg. one or several NO-synthase
     inhibitors and one or several metabolic antioxidants intervening in the
     redox status of the thiol groups, as a combined product in a sepd. form of
     said active ingredients.  A mixt. of 3 mg/kg N-phenyl-
     2-thiophenecarboximidamine and 10 mg/kg lipoic acid
     increased the dopamine level in guinea pigs suffering from parkinson to
     5.21 ng/mg nervous tissue which was higher than either compds.
AN   133:276363  CA
```

TI Association of NO-synthase inhibitors and metabolic antioxidants
IN Auguet, Michel; Harnett, Jeremiah; Chabrier De Lassauniere, Pierre-etienne
PA Societe de Conseils de Recherches et d'Applications Scientifiques (S.C.R.A.S, Fr.
SO PCT Int. Appl., 16 pp.
CODEN: PIXXD2
DT Patent
LA French
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000059448	A2	20001012	WO 2000-FR812	20000331
	WO 2000059448	A3	20010308		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	FR 2791571	A1	20001006	FR 1999-4134	19990402
	FR 2791571	B1	20021004		
	EP 1169005	A2	20020109	EP 2000-915262	20000331
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	NO 2001004770	A	20011123	NO 2001-4770	20011001
PRAI	FR 1999-4134	A	19990402		
	WO 2000-FR812	W	20000331		

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=> s N-phenyl-2-thiophenecarboximidamine
59362 N
6010 PHENYL
77098 2

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              0 THIOPHENECARBOXIMIDAMINE
L2            0 N-PHENYL-2-THIOPHENECARBOXIMIDAMINE
                (N(W)PHENYL(W)2(W)THIOPHENECARBOXIMIDAMINE)

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COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
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FULL ESTIMATED COST                                     6.96      17.65

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in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

=> s N-phenyl-2-thiophenecarboximidamine/cn
L3            0 N-PHENYL-2-THIOPHENECARBOXIMIDAMINE/CN
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L5           23 SEA FILE=HCAPLUS ABB=ON  (L1 OR PHENYL?(W)2(W)?THIOPHENECARBOXI
                MID? OR ?PHENYL2THIOPHENECARBOXIMID?)

=> d 15 ibib abs hitstr 1-23

L5   ANSWER 1 OF 23  HCAPLUS  COPYRIGHT 2003 ACS
ACCESSION NUMBER:         2002:185107  HCAPLUS
DOCUMENT NUMBER:          136:247484
TITLE:                    Preparation of furan and thiophene amidine derivatives
                          useful as inhibitors of nitric oxide synthase
INVENTOR(S):              Chen, Deborah; Empfield, James; Mattes, Kenneth;
                          Murray, Robert; Phillips, Eifion
PATENT ASSIGNEE(S):       Astrazeneca AB, Swed.
SOURCE:                   PCT Int. Appl., 47 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.          KIND  DATE            APPLICATION NO.   DATE
     ----------------    ----  --------        --------------    --------
     WO 2002020511        A1   20020314        WO 2001-SE1868    20010830
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
             CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
             GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
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             PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG,
             US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
             DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,
             BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
     AU 2001082829        A5   20020322        AU 2001-82829     20010830
PRIORITY APPLN. INFO.:                      GB 2000-21705     A  20000905
                                            GB 2000-21706     A  20000905
                                            SE 2001-2156      A  20010614
                                            WO 2001-SE1868    W  20010830

OTHER SOURCE(S):          MARPAT 136:247484
GI
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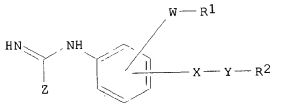


I

AB Amidine derivs. [I; wherein Z = furan or thiophene ring (optionally substituted); X = (C1-C6)alkyl or CO; Y = O, S(O)a, or NR3 (wherein a = 0, 1, or 2; R3 = H, (C1-C6)alkyl, Ph, etc.); W = S(O)c (wherein c = 0, 1, or

2); R2 = H, (Cl-C6)alkyl, Ph, etc.] were prepd. Thus, a mixt. of [3-(chloromethyl)-4-(methylsulfanyl)**phenyl**]-2-**thiophenecarboximidamide** hydrochloride, isopropylamine, and diisopropylethylamine in DMF was stirred at room temp. for 16 h to give 70% N-[3-[[isopropylamino]methyl]-4-[methylsulfanyl]**phenyl**]-**2-thiophenecarboximidamide**. The prepd. compds. showed IC50 <10 .mu.M for inhibition of neuronal nitric oxide synthase.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 2 OF 23 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2001:472695 HCAPLUS

DOCUMENT NUMBER: 135:76782

TITLE: Amidine derivatives which are inhibitors of nitric oxide synthase

INVENTOR(S): Mattes, Kenneth; Murray, Robert; Phillips, Eifion; Schmitthenner, Hans

PATENT ASSIGNEE(S): Astrazeneca AB, Swed.

SOURCE: PCT Int. Appl., 70 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

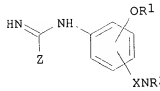
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001046170	A1	20010628	WO 2000-SE2539	20001214
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 2002137736	A1	20020926	US 2001-763835	20010227
PRIORITY APPLN. INFO.:			SE 1999-4676 A	19991220
			WO 2000-SE2539 W	20001214

OTHER SOURCE(S): MARPAT 135:76782

GI



I

AB Amidines I [Z = (un)substituted furyl or thienyl; R1 = H, alkyl, alkoxyalkyl, aminoalkyl, etc.; X = alkyl; NR2R3 = NH2, azetidinyl, pyrrolidinyl, piperidinyl, morpholinyl, etc.] were prepd. and showed IC50 values of <10 .mu.M for inhibition of neuronal nitric oxide synthase. Thus, N-[4-methoxy-3-[(methylamino)methyl]**phenyl**]-2-**thiophenecarboximidamide** dihydrochloride was prepd. in 3 steps starting from 2-methoxy-5-nitrobenzaldehyde and MeNH2 and proceeding via

4-methoxy-3-[(methylamino)methyl]aniline hydrochloride.
REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 3 OF 23 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:380573 HCAPLUS
DOCUMENT NUMBER: 134:366792
TITLE: Preparation of novel amidine derivatives as NO synthase and/or monoamine oxydase inhibitors
INVENTOR(S): Chabrier De Lassauniere, Pierre-Etienne; Harnett, Jeremiah
PATENT ASSIGNEE(S): Societe de Conseils de Recherches et d'Applications Scientifiques (S.C.R.A.S.), Fr.
SOURCE: PCT Int. Appl., 29 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001036407	A1	20010525	WO 2000-FR3168	20001115
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
FR 2801053	A1	20010518	FR 1999-14334	19991116
EP 1233957	A1	20020828	EP 2000-979732	20001115
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				

PRIORITY APPLN. INFO.: FR 1999-14334 A 19991116
WO 2000-FR3168 W 20001115

OTHER SOURCE(S): MARPAT 134:366792
AB Amidine derivs., useful for prepg. a medicine designed to inhibit NO synthases and/or monoamine oxydases, were prepd. Thus, N'-(4-{[methyl(2-propynyl)amino]methyl}**phenyl**)-2-**thiophenecarboximidamide**; N'-(4-{[methyl(cyanomethyl)amino]methyl}**phenyl**)-2-**thiophenecarboximidamide**; N'-(4-{[methyl(propyl)amino]methyl}**phenyl**)-2-**thiophenecarboximidamide**; N'-(4-{[methyl(3-cyanoethyl)amino]methyl}**phenyl**)-2-**thiophenecarboximidamide**; and N'-(4-{[methyl(4-pentynyl)amino]methyl}**phenyl**)-2-**thiophenecarboximidamide** were prepd.
REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 4 OF 23 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:338385 HCAPLUS
DOCUMENT NUMBER: 134:348264
TITLE: Product comprising at least a NO synthase inhibiting substance associated with at least a phospholipase A2 inhibiting substance
INVENTOR(S): Auguet, Michel; Chabrier de Lassauniere,

Pierre-Etienne
PATENT ASSIGNEE(S): Societe de Conseils de Recherches et d'Applications Scientifiques (S.C.R.A.S.), Fr.
SOURCE: PCT Int. Appl., 37 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

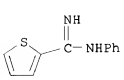
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001032216	A2	20010510	WO 2000-FR3066	20001103
WO 2001032216	A3	20020328		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
FR 2800615	A1	20010511	FR 1999-13859	19991105
FR 2800615	B1	20020503		
EP 1233786	A2	20020828	EP 2000-974645	20001103
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				

PRIORITY APPLN. INFO.: FR 1999-13859 A 19991105
WO 2000-FR3066 W 20001103

AB The invention concerns a product comprising at least a NO synthase inhibiting substance assocd. with at least a phospholipase A2 inhibiting substance, sep. or combined, for simultaneous therapeutic use, sep. or spread over time for treating pathologies in which nitrogen monoxide and/or phosplipases A2 are involved. The invention also concerns a pharmaceutical compn. comprising, as active principle, at least a NO synthase inhibiting substance and at least a phospholipase A2 inhibiting substance, and optionally a pharmaceutically acceptable carrier. Administration of 25 mg 7-nitroindazole/kg and 30 mg mepacrine/kg in rats had synergistic effect and reduced the carrageenin-induced inflammation significantly.

IT **3737-39-1**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(product comprising at least NO synthase inhibiting substance assocd. with at least phospholipase A2 inhibiting substance)

RN 3737-39-1 HCAPLUS
CN 2-Thiophenecarboximidamide, N-phenyl- (9CI) (CA INDEX NAME)



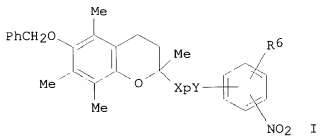
L5 ANSWER 5 OF 23 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2001:185743 HCAPLUS
DOCUMENT NUMBER: 134:237392
TITLE: Preparing amidines derived from 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid
INVENTOR(S): Le Breton, Christine; Manginot, Eric; Cazaux, Jean-Bernard
PATENT ASSIGNEE(S): Societe D'expansion Scientifique Expansia, Fr.
SOURCE: PCT Int. Appl., 21 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001017987	A1	20010315	WO 2000-FR2417	20000901
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
FR 2798127	A1	20010309	FR 1999-11044	19990903
EP 1214309	A1	20020619	EP 2000-960773	20000901
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				

PRIORITY APPLN. INFO.: FR 1999-11044 A 19990903
WO 2000-FR2417 W 20000901

OTHER SOURCE(S): MARPAT 134:237392
GI



I

AB The invention concerns the use of novel intermediates of general formula I (defined below) for the synthesis of amidines derived from (-)-6-hydroxy-2,5,7,8 tetramethylchroman-2-carboxylic acid, such as for example, (S)-N-{4-[4-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)-carbonyl]-1-piperazinyl]**phenyl**}-2-**thiophenecarboximidamide**. In general formula I: X represents Z1CO; .rho. represents a bond or a heterocycle selected among the group consisting of piperidine, piperazine, homopiperazine, 2-methylpiperazine, 2,5-dimethyl-piperazine, or 4-aminopiperidine radicals; Y represents a radical selected among the Z2 and NR3Z2 radicals; R3 represents a hydrogen atom, a linear or branched alkyl radical with 1 to 6 carbon atoms or a

COR4 radical; R4 represents a linear or branched alkyl radical with 1 to 6 carbon atoms; Z1 and Z2 independently represent a single bond or a linear or branched alkyl radical with 1 to 6 carbon atoms; and R6 represents a hydrogen atom or a OH group.

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 6 OF 23 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:725417 HCAPLUS
DOCUMENT NUMBER: 133:276363
TITLE: Association of NO-synthase inhibitors and metabolic antioxidants
INVENTOR(S): Auguet, Michel; Harnett, Jeremiah; Chabrier De Lassauniere, Pierre-etienne
PATENT ASSIGNEE(S): Societe de Conseils de Recherches et d'Applications Scientifiques (S.C.R.A.S, Fr.
SOURCE: PCT Int. Appl., 16 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

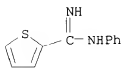
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000059448	A2	20001012	WO 2000-FR812	20000331
WO 2000059448	A3	20010308		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
FR 2791571	A1	20001006	FR 1999-4134	19990402
FR 2791571	B1	20021004		
EP 1169005	A2	20020109	EP 2000-915262	20000331
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
NO 2001004770	A	20011123	NO 2001-4770	20011001

PRIORITY APPLN. INFO.: FR 1999-4134 A 19990402
WO 2000-FR812 W 20000331

AB The invention relates to a pharmaceutical compn. comprising as an active ingredient one or several substances interfering with the synthesis of nitrogen monoxide by inhibiting NO-synthase and one or several metabolic antioxidants contg. thiol groups and intervening in the redox status of the thiol groups, and optionally a pharmaceutically acceptable support. The invention also relates to a product contg. one or several NO-synthase inhibitors and one or several metabolic antioxidants intervening in the redox status of the thiol groups, as a combined product in a sepd. form of said active ingredients. A mixt. of 3 mg/kg N-**phenyl-2-thiophenecarboximidamine** and 10 mg/kg lipoic acid increased the dopamine level in guinea pigs suffering from parkinson to 5.21 ng/mg nervous tissue which was higher than either compds.

IT **3737-39-1**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(assocn. of NO-synthase inhibitors and metabolic antioxidants)
RN 3737-39-1 HCAPLUS
CN 2-Thiophenecarboximidamide, N-phenyl- (9CI) (CA INDEX NAME)



L5 ANSWER 7 OF 23 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:616235 HCAPLUS
DOCUMENT NUMBER: 134:127858
TITLE: Radiolabeled neuronal nitric oxide synthase inhibitors: synthesis, in vivo evaluation, and primate PET studies
AUTHOR(S): Pomper, Martin G.; Musachio, John L.; Scheffel, Ursula; Macdonald, James E.; McCarthy, Dennis J.; Reif, David W.; Villemagne, Victor L.; Yokoi, Fuji; Dannals, Robert F.; Wong, Dean F.
CORPORATE SOURCE: Department of Radiology, Johns Hopkins University School of Medicine, Baltimore, MD, 21287-2182, USA
SOURCE: Journal of Nuclear Medicine (2000), 41(8), 1417-1425
CODEN: JNMEAQ; ISSN: 0161-5505
PUBLISHER: Society of Nuclear Medicine, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The objectives of this study were to synthesize neuronal nitric oxide synthase (NOS-I)-selective imaging agents based on the 2 potent, selective inhibitors AR-R 17443 [N-(4-((2-((phenylmethyl)(methyl)- amino)ethyl) **phenyl)-2-thiophenecarboximidamide**)] and AR-R 18512 [(N-(2-methyl-1,2,3,4-tetrahydroisoquinoline-7-yl)-2-thiophenecarboximidamide)] in positron-emitting form and to evaluate regional brain uptake in rodents and primates. Methods: [11C]AR-R 17443 and [11C]AR-R 18512 were produced by N-alkylation of the corresponding desmethyl precursors using [11C]iodomethane. Regional brain uptake of [11C]AR-R 17443 and [11C]AR-R 18512 was assayed in rats and NOS-I knockout mice, and PET was performed in baboons. Tracer kinetic modeling used a 2-compartment plasma and brain tissue model. Results: Yields of [11C]AR-R 17443 and [11C]AR-R 18512 ranged from 8% to 16% at the end of synthesis, with specific activities of 50-178 GBq/.mu.mol (1350-4800 Ci/mmol) at the end of synthesis. In rat cerebellum and cortex at 30 min after injection, [11C]AR-R 17443 showed 1.01 .+-. 0.01 and 1.63 .+-. 0.12 percentage injected dose per g (%ID/g) uptake, resp., whereas [11C]AR-R 18512 showed 0.88 .+-. 0.01 and 1.30 .+-. 0.07 %ID/g uptake, resp. Attempts to block tracer uptake by pretreatment with the NOS-I-selective inhibitor 7-nitroindazole or the corresponding unlabeled inhibitor (or desmethyl precursor to AR-R 17443 of similar potency) were unsuccessful. A small but significant (20%) decrease in cerebellar uptake of [11C]AR-R 18512 was present in NOS-I knockout mice compared with control mice. PET of [11C]AR-R 18512 in baboons with concurrent regional cerebral blood flow (rCBF) detn. before and after administration of blocker showed dose-related decreases in cerebellar uptake that were greater than or equal to decreases in rCBF. Plasma metabolites accounted for 27% of total activity at 30 min after injection. Kinetic modeling of binding potentials revealed a distribution vol. of 334 in cerebral blood that dropped 51% after blocker administration. Conclusion: Rodent studies for

[11C]AR-R 17443 and [11C]AR-R 18512 showed little evidence of specific NOS-I binding. In baboons, we detected a higher uptake of [11C]AR-R 18512 in the cerebellum than in the cortex (approx. 5%, accounting for decreased rCBF because of blockade), indicating minimal specific binding. Analogs of higher affinity are likely required if this class of agents is to prove viable for PET.

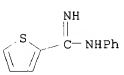
REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 8 OF 23 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:531382 HCAPLUS
DOCUMENT NUMBER: 133:261397
TITLE: Discovery and development of neuronal nitric oxide synthase inhibitors
AUTHOR(S): Reif, D. W.; McCarthy, D. J.; Cregan, E.; Macdonald, J. E.
CORPORATE SOURCE: AstraZeneca R and D Boston, Worcester, MA, USA
SOURCE: Free Radical Biology & Medicine (2000), 28(10), 1470-1477
CODEN: FRBMEH; ISSN: 0891-5849
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The role of neuronally derived nitric oxide (NO) in neurotransmission and neural injury remains an area of active investigation. NO generation has been postulated to be involved in the deleterious events surrounding ischemia/reperfusion injury either directly or via the prodn. of more reactive oxidants such as peroxynitrite. In our search for novel therapeutics for the treatment of a variety of neurol. diseases including stroke, we have discovered novel, potent, and selective inhibitors of the neuronal nitric oxide synthase (nNOS) isoform. These compds. have proven to be effective in models of ischemia/reperfusion supporting the role of nNOS in these processes. The effects of these compds. as well as addnl. aspects crit. to their development will be presented.

IT **3737-39-1**, AR-R 16444
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(discovery and development of neuronal nitric oxide synthase inhibitors)

RN 3737-39-1 HCAPLUS
CN 2-Thiophenecarboximidamide, N-phenyl- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 9 OF 23 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:490358 HCAPLUS
DOCUMENT NUMBER: 133:202864
TITLE: ARL 17477, a selective nitric oxide synthase inhibitor, with neuroprotective effects in animal models of global and focal cerebral ischemia

AUTHOR(S): O'Neill, M. J.; Murray, T. K.; McCarty, D. R.; Hicks, C. A.; Dell, C. P.; Patrick, K. E.; Ward, M. A.; Osborne, D. J.; Wiernicki, T. R.; Roman, C. R.; Lodge, D.; Fleisch, J. H.; Singh, J.
CORPORATE SOURCE: Lilly Research Centre, Eli Lilly and Co. Ltd., Windlesham, Surrey, GU20 6PH, UK
SOURCE: Brain Research (2000), 871(2), 234-244
CODEN: BRREAP; ISSN: 0006-8993
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In the present studies, we have evaluated the effects of N-[4-(2-{[(3-Chlorophenyl)methyl]amino)ethyl)**phenyl**]-2**-thiophenecarboximidamide** dihydrochloride (ARL 17477) on recombinant human neuronal NOS (nNOS) and endothelial NOS (eNOS). We then carried out pharmacokinetic studies and measured cortical nitric oxide synthase (NOS) inhibition to det. that the compd. crossed the blood brain barrier. Finally, the compd. was evaluated in a model of global ischemia in the gerbil and two models of transient focal ischemia in the rat. The IC50 values for ARL 17477 on human recombinant human nNOS and eNOS were 1 and 17 .mu.M, resp. ARL 17477 (50 mg/kg i.p.) produced a significant redn. in the ischemia-induced hippocampal damage following global ischemia when administered immediately post-occlusion, but failed to protect when administration was delayed until 30 min post-occlusion. In the endothelin-1 model of focal ischemia, ARL 17477 (1 mg/kg i.v.) significantly attenuated the infarct vol. when administered at either 0, 1 or 2 h post-endothelin-1 (P<0.05). In the intraluminal suture model, ARL 17477 at both 1 and 3 mg/kg i.v. failed to reduce the infarct vol. measured at 1, 3 or 7 days post-occlusion. These results demonstrate that ARL 17477 protects against global ischemia in gerbils and provides some redn. in infarct vol. following transient middle cerebral artery occlusion in rats, indicating that nNOS inhibition may be a useful treatment of ischemic conditions.

REFERENCE COUNT: 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 10 OF 23 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:704431 HCAPLUS
DOCUMENT NUMBER: 131:317686
TITLE: Synergistic neuroprotective effects by combining an NMDA or AMPA receptor antagonist with nitric oxide synthase inhibitors in global cerebral ischemia
AUTHOR(S): Hicks, C. A.; Ward, M. A.; Swettenham, J. B.; O'Neill, M. J.
CORPORATE SOURCE: Lilly Research Centre, Eli Lilly & Company, Windlesham, Surrey, UK
SOURCE: European Journal of Pharmacology (1999), 381(2/3), 113-119
CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We have investigated the neuroprotective effects of combining an NMDA or AMPA receptor antagonist with a nitric oxide synthase (NOS) inhibitor in the gerbil model of global cerebral ischemia. Ischemia was induced by occlusion of the common carotid arteries for 5 min. (5R,10S)-(+)-5-methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine (MK-801, 2.5 mg/kg i.p.) or (3S,4aR,6R,8aR)-6-[2-(1(2)H-tetrazole-5-yl)]decahydroisoquinoline-3-carboxylic acid (LY293558, 20 mg/kg i.p.) and 7-nitroindazole (25 mg/kg i.p.) or N-[4-(2-{[(3-chlorophenyl)methyl]amino}ethyl) **phenyl**]-

2-thiophenecarboximidamide dihydrochloride (ARL17477, 25 mg/kg i.p.) were administered alone or in combination (i.e., MK-801 with 7-nitroindazole or ARL17477 or LY293558 with 7-nitroindazole or ARL17477). In the present studies, both MK-801 and LY293558 provided significant degree of neuroprotection, while 7-nitroindazole and ARL17477 also provided some neuroprotection, which failed to reach significance in every case. However, the combination of MK-801 with 7-nitroindazole or ARL17477 provided 21% or 44% greater protection than the total protection or either alone. Likewise, the combination of LY293558 with 7-nitroindazole or ARL17477 provided 14.5% and 35% greater protection than total protection of either compd. alone. These results indicate that several pathways contribute to ischemic cell death and combining excitatory amino antagonists and NOS inhibitors provides greater protection than either alone. Therefore, combination therapy should be considered as an approach for treating ischemic conditions.

REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 11 OF 23 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:616023 HCAPLUS
DOCUMENT NUMBER: 131:346378
TITLE: BN 80933, a dual inhibitor of neuronal nitric oxide synthase and lipid peroxidation: a promising neuroprotective strategy
AUTHOR(S): Chabrier, Pierre-Etienne; Auguet, Michel; Spinnewyn, Brigitte; Auvin, Serge; Cornet, Sylvie; Demerle-Pallardy, Caroline; Guilmard-Favre, Christine; Marin, Jean-Gregoire; Pignol, Bernadette; Gillard-Roubert, Veronique; Roussillot-Charnet, Christelle; Schulz, Jocelyne; Viossat, Isabelle; Bigg, Dennis; Moncada, Salvador
CORPORATE SOURCE: Beaufour-Ipsen Research Laboratories, Institut Henri Beaufour, Les Ulis, 91966, Fr.
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (1999), 96(19), 10824-10829
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Nitric oxide (NO) and reactive oxygen species (ROS) act independently as well as cooperatively to induce neuronal death in acute neurol. disorders. Inhibition of neuronal nitric oxide synthase (nNOS) and inhibition of lipid peroxidn. induced by ROS have both been proposed as neuroprotective strategies in stroke and trauma. Recently, in our lab., the combination of the two strategies was found to be synergistic in reducing neuronal damage. Here, we report that BN 80933 [(S)-N-[4-[4-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)carbonyl]-1-piperazinyl] **phenyl**]-**2-thiophenecarboximidamide**], a compd. that combines potent antioxidant and selective nNOS inhibitory properties in vitro, affords remarkable neuronal protection in vivo. I.v. administration of BN 80933 significantly reduced brain damage induced by head trauma in mice, global ischemia in gerbils, and transient focal ischemia in rats. Treatment with BN 80933 (0.3-10 mg/kg) significantly reduced infarct vol. (>60% protection) and enhanced behavioral recovery in rats subjected to transient (2-h) middle cerebral artery occlusion and 48-h or 7-day reperfusion. Furthermore, treatment with BN 80933 commencing up to 8 h after the onset of ischemia resulted in a significant improvement of neurol. outcome. All these results indicate that BN 80933 represents a class of potentially useful therapeutic agents for the treatment of stroke or trauma and possibly neurodegenerative disorders

that involve both NO and ROS.
REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 12 OF 23 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:169475 HCAPLUS
DOCUMENT NUMBER: 128:248580
TITLE: Association of NO synthase inhibitors with trappers of reactive oxygen species
INVENTOR(S): Chabrier De Lassauniere, Pierre-Etienne; Bigg, Denis
PATENT ASSIGNEE(S): Societe De Conseils De Recherches Et D'applications Scientifiques (S.C.R.A.S, Fr.; Chabrier De Lassauniere, Pierre-Etienne; Bigg, Denis
SOURCE: PCT Int. Appl., 22 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

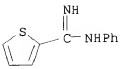
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9809653	A1	19980312	WO 1997-FR1567	19970905
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
FR 2753098	A1	19980313	FR 1996-10875	19960906
FR 2753098	B1	19981127		
AU 9742111	A1	19980326	AU 1997-42111	19970905
AU 734296	B2	20010607		
EP 939654	A1	19990908	EP 1997-940183	19970905
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2000517336	T2	20001226	JP 1998-512314	19970905
RU 2174844	C2	20011020	RU 1999-106792	19970905
US 6297281	B1	20011002	US 1999-254254	19990302
NO 9901100	A	19990505	NO 1999-1100	19990305

PRIORITY APPLN. INFO.: FR 1996-10875 A 19960906
WO 1997-FR1567 W 19970905

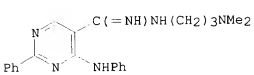
AB The invention concerns a pharmaceutical compn. contg., as active principle, at least one NO synthase-inhibiting substance and at least one reactive oxygen-trapping substance, optionally with a pharmaceutically acceptable support. The invention also concerns a product contg. at least one NO synthase-inhibiting substance and at least one reactive oxygen-trapping substance as combined product of these active principles in sep. form.

IT **3737-39-1**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(assocn. of NO synthase inhibitors with trappers of reactive oxygen species)

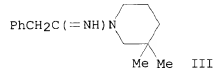
RN 3737-39-1 HCAPLUS
CN 2-Thiophenecarboximidamide, N-phenyl- (9CI) (CA INDEX NAME)



L5 ANSWER 13 OF 23 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1991:550200 HCAPLUS
DOCUMENT NUMBER: 115:150200
TITLE: Influence of some substituted aromatic amidines on monoamine oxidase activity
AUTHOR(S): Robev, S.; Tsanova, Ts.
CORPORATE SOURCE: Fac. Med., Sofia, 1431, Bulg.
SOURCE: Dokladi na Bulgarskata Akademiya na Naukite (1991), 44(1), 67-9
CODEN: DBANEH; ISSN: 0861-1459
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



II

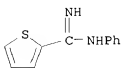


III

AB 2,6-R2C6H4N:CR1NH2 (R = Cl, Me, Et, R1 = 4-pyridyl; R = Me, R1 = Ph; R = H, R1 = substituted Ph), 4-R2C6H4CH2C(:NH)NHC6H4R3-4 (I, R2 = H, Cl; R3 = H, F, Me), pyrimidine II, and piperidine III caused 30-80% inhibition of monoamine oxidase at 3 .times. 10-2 M in vitro. I (R2 = Cl, R3 = Me) was most active.

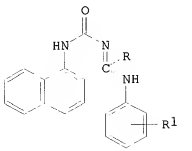
IT **3737-39-1**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(monoamine oxidase-inhibiting activity of)

RN 3737-39-1 HCAPLUS
CN 2-Thiophenecarboximidamide, N-phenyl- (9CI) (CA INDEX NAME)

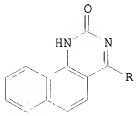


L5 ANSWER 14 OF 23 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1988:528942 HCAPLUS
DOCUMENT NUMBER: 109:128942
TITLE: Quinazolone synthesis from N-aryl-N'-arylaminoformylated amidines
AUTHOR(S): Robev, S.
CORPORATE SOURCE: Med. Fac., Sofia, 1431, Bulg.

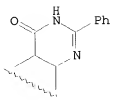
SOURCE: Doklady Bolgarskoi Akademii Nauk (1987), 40(12), 41-4
CODEN: DBANAD; ISSN: 0366-8681
DOCUMENT TYPE: Journal
LANGUAGE: Russian
OTHER SOURCE(S): CASREACT 109:128942
GI



I



II

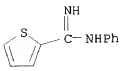


III

AB Refluxing amidines I (R = H, 2-thenoyl, 4-chlorobenzoyl, 4-toluoyl, R1 = Ph, 4-tolyl, 2,6-xylyl, PhCH2) in DMF gave benzoquinazolones II. Addn. of PhCH2C(:NH)NHPh with PhNCO gave PhCH2(:NH)N(CONHPh)Ph which on heating decompd. to give 1,3-diphenylurea and PhCH2CN. Addnl. obtained was benzoquinazolone III.

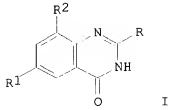
IT **3737-39-1**
RL: RCT (Reactant); RACT (Reactant or reagent)
(addn. reaction of, with naphthyl isocyanate)

RN 3737-39-1 HCAPLUS
CN 2-Thiophenecarboximidamide, N-phenyl- (9CI) (CA INDEX NAME)



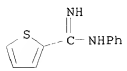
L5 ANSWER 15 OF 23 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1984:571199 HCAPLUS
DOCUMENT NUMBER: 101:171199
TITLE: A new method for preparation of 2-aryl-substituted quinazoline-4(3H)-ones
AUTHOR(S): Robeva, A.; Robev, S.
CORPORATE SOURCE: Dep. Pharmacol., Med. Fac., Sofia, 1431, Bulg.
SOURCE: Doklady Bolgarskoi Akademii Nauk (1984), 37(3), 337-40
CODEN: DBANAD; ISSN: 0366-8681

DOCUMENT TYPE: Journal
LANGUAGE: English
GI

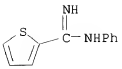


I

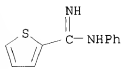
AB N-Arylamidines were treated with ClCO2Et to yield quinazolinones I (R = Cl2C6H3, Ph, thienyl, biphenylyl; R1 = H, Me, Cl; R2 = H, Me). Thus, 3,4-Cl2C6H3C(NH2):NC6H4Me-4 was heated with ClCO2Et in quinoline to give I (R = 3,4-Cl2C6H3, R1 = Me, R2 = H).
IT **3737-39-1**
RL: RCT (Reactant); RACT (Reactant or reagent)
(cyclocondensation of, with chloroformate ester)
RN 3737-39-1 HCAPLUS
CN 2-Thiophenecarboximidamide, N-phenyl- (9CI) (CA INDEX NAME)



L5 ANSWER 16 OF 23 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1976:577373 HCAPLUS
DOCUMENT NUMBER: 85:177373
TITLE: Synthesis of polynitrogen heterocycles from furan, thiophene, and selenophene nitriles or imino ethers
AUTHOR(S): Decroix, B.; Dubus, P.; Morel, J.; Pastour, P.
CORPORATE SOURCE: Lab. Chim. Org. Heterocycles, Inst. Sci. Haute-Normandie, Mont-Saint-Aignan, Fr.
SOURCE: Bulletin de la Societe Chimique de France (1976), (3-4, Pt. 2), 621-7
CODEN: BSCFAS; ISSN: 0037-8968
DOCUMENT TYPE: Journal
LANGUAGE: French
AB Benzimidazoles, triazoles, tetrazoles, and tetrazines with furyl, thienyl, and selenienyl substituents were prepd. from RCN (R = 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-selenienyl, 3-selenienyl) and N2H4 or NaN3 or via RC(:NH)OEt.
IT **3737-39-1P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of)
RN 3737-39-1 HCAPLUS
CN 2-Thiophenecarboximidamide, N-phenyl- (9CI) (CA INDEX NAME)



L5 ANSWER 17 OF 23 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1974:505150 HCAPLUS
DOCUMENT NUMBER: 81:105150
TITLE: Preparation and reactions of N-ethoxycarbonylthiophene-2-carboxamide and N-ethoxycarbonylthiophene-2-thiocarboxamide
AUTHOR(S): Papadopoulos, E. P.
CORPORATE SOURCE: Dep. Chem., Univ. New Mexico, Albuquerque, NM, USA
SOURCE: Journal of Organic Chemistry (1974), 39(17), 2540-2
CODEN: JOCEAH; ISSN: 0022-3263
DOCUMENT TYPE: Journal
LANGUAGE: English
GI For diagram(s), see printed CA Issue.
AB In the presence of anhydrous SnCl4, thiophene reacts with EtO2CNCO and EtO2CNCS to yield the title compds. I (X = O, S), which were reactive toward nucleophilic reagents at both carbonyl and thiocarbonyl groups.
IT **3737-39-1P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of)
RN 3737-39-1 HCAPLUS
CN 2-Thiophenecarboximidamide, N-phenyl- (9CI) (CA INDEX NAME)



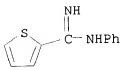
L5 ANSWER 18 OF 23 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1964:477907 HCAPLUS
DOCUMENT NUMBER: 61:77907
ORIGINAL REFERENCE NO.: 61:13613d-f
TITLE: A comparative study of the effect of radiation epilation in mice treated before irradiation with cysteamine and N-phenylamidines of pyromucic and 2-thiophenecarboxylic acids
AUTHOR(S): Kaneti, Ya.; Robev, St.
SOURCE: Nauchni Tr. Inst. Spets. Usuvurshenst. Lekarite (1961), 8(2), 31-4
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable
AB Some substituted aromatic amidines possess distinct radioprotective properties in mice and some bacteria. Since these compds. are structurally different from known radioprotective substances, the possibility was considered that they act by a different mechanism. Local contact irradiation of mice treated with 3 mg. cysteamine-HCl (3% soln. recrystd. from alc. in a Hatm.), 1 mg. LFA (N-phenylpyromucamidine), or 1 mg. LTA (N-phenyl-2-thiophenecarboxamidine) as a 1% soln. in dil. HOAc at pH 5 and

irradiated with the Schaul app. revealed that there was no difference between the controls and mice pretreated with LTA or LFA, and after pretreatment with cysteamine only 50% epilation occurred during the observation period of 20 days. Complete epilation of the irradiated area was considered a pos. effect. These findings support the assumption that the amidines, which have good radioprotective activity for totally irradiated mice, do not act the same way as SH-contg. substances.

IT **3737-39-1**, 2-Thiophenecarboxamidine, N-phenyl-
(in radiation-damage prevention, a comparison with cysteamine)

RN 3737-39-1 HCAPLUS

CN 2-Thiophenecarboximidamide, N-phenyl- (9CI) (CA INDEX NAME)



L5 ANSWER 19 OF 23 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1964:463028 HCAPLUS

DOCUMENT NUMBER: 61:63028

ORIGINAL REFERENCE NO.: 61:10981d-e,10982a-c

TITLE: An investigation of the influence of N-phenylbenzamidine, N-phenyl-2-furamidine and the N-phenylamidine of thiophene-2-carboxylic acid on the radiation resistance of suspensions of Bacillus anthracis, B. cereus, Candida albicans and Staphylococcus aureus in irradiation with .gamma. rays

AUTHOR(S): Robev, St.; Todorov, Sv.

SOURCE: Nauchni Tr. Inst. Spets. Usuvurshenst. Lekarite (1961), 8(2), 35-41

DOCUMENT TYPE: Journal

LANGUAGE: Unavailable

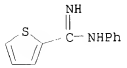
AB cf. CA 54, 19841b. Amidines, because of their chem. configuration which allows the introduction of a no. of structural variations, and which differ from other known radio-protectives, represent a great interest in studying the radioprotective mechanism in general. Bacterial suspensions of B. anthracis, B. cereus, C. albicans and S. aureus, obtained from 20hr. horizontal agar culture, were irradiated with Co and the no. of surviving bacteria capable of forming colonies were used for evaluation of the radiation effect. The following amidines, synthesized from the corresponding aldehyde arylhydrazones, were investigated: N-phenylbenzamidine (NPA), m.p. 114-15.degree., N-phenyl-2-furamidine (.alpha.-FA) m.p. 106-7.degree., and the N-phenylamidine of thiophene-2-carboxylic acid (.alpha.-TA) m.p. 144-5.degree.. The radiosensitivity of B. anthracis and B. cereus is not changed by the amidines after .gamma.-radiation of 300,000 r. A noticeable radioprotection is observed with a cell suspension of C. albicans at dilns. of 1:500 up to 1:2500. On the other hand, amidines act as radiosensitizers toward S. aureus 209, .alpha.-FA having the strongest effect, starting at a diln. of 1:3000 and remaining const. up to a diln. of 1:30,000. The lack of activity of the amidines toward the 4 microorganisms could be explained by a decreased penetration permeability of the cell membrane, which is supported by the fact that even at very high concns. of NPA, no changes in the microbial population occur, and it is unlikely that the amidines are inactive in the inner cell. The sensitizing properties of .alpha.-FA against S. aureus and its

radioprotective properties against other types would indicate that an increase or decrease in radiation resistance by a chem. compd. are not isolated properties; there is a connection between the two, and there could be a possible transition from one to the other. The possibility of the sensitizing properties being connected with the furan ring has been further investigated with S. aureus with furfurol and pyromucic acid. The former has no radioprotective effect and the latter shows a toxic effect at dilns. up to 1:800; at further diln. S. aureus remains completely indifferent regarding toxicity or radioprotection.

IT **3737-39-1**, 2-Thiophenecarboxamidine, N-phenyl-
(effect on bacterial resistance to .gamma.-irradiation)

RN 3737-39-1 HCAPLUS

CN 2-Thiophenecarboximidamide, N-phenyl- (9CI) (CA INDEX NAME)



L5 ANSWER 20 OF 23 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1962:437637 HCAPLUS

DOCUMENT NUMBER: 57:37637

ORIGINAL REFERENCE NO.: 57:7574a-c

TITLE: Influence of the N-phenylamidine of thiophene-2 carboxylic acid on the bone-marrow changes in acute radiation sickness

AUTHOR(S): Zografov, D. G.; Baev, Il.

CORPORATE SOURCE: Radiobiol. Abteilung, Sofia, Bulg.

SOURCE: Acta Biol. Med. Ger. (1962), 8, 337-43

DOCUMENT TYPE: Journal

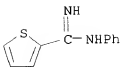
LANGUAGE: German

AB Treatment of rats with the N-phenylamidine of thiophene-2-carboxylic acid (I) before x-ray radiation with 650 r. reduced the damage to bone marrow cells and caused faster recovery. Male rats were divided into 4 groups: (1) 25 untreated controls, (2) 15 treated with I and not irradiated, (3) 30 treated with 5 mg./100 g. body wt. of a 0.1% soln. of I in HOAc 5 min. before radiation, (4) 30 irradiated without I. Group 2 showed that I alone has no significant effect on the bone marrow. Five rats each from groups 3 and 4 were killed at day 1-30 and the bone marrow examd. to det. the mitosis index, maturation index of the granulocytes and the erythroblasts, and the percentage of blood cells, reticulocytes, granulocytes, erythroblasts, lymphocytes, and megakaryocytes. In each case the radiation damage was less and recovery began earlier and proceeded faster in group 3 than in group 4 except that the lymphocytes showed no protection by I.

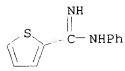
IT **3737-39-1**, 2-Thiophenecarboxamidine, N-phenyl-
(effect on bone marrow in radiation sickness)

RN 3737-39-1 HCAPLUS

CN 2-Thiophenecarboximidamide, N-phenyl- (9CI) (CA INDEX NAME)

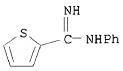


L5 ANSWER 21 OF 23 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1962:424658 HCAPLUS
DOCUMENT NUMBER: 57:24658
ORIGINAL REFERENCE NO.: 57:4990e-f
TITLE: Radioprotective effects of certain amidines on rats preliminarily treated with zymosan
AUTHOR(S): Nikolov, I.
SOURCE: Compt. Rend. Acad. Bulgare Sci. (1961), 14, 659-62
DOCUMENT TYPE: Journal
LANGUAGE: English
AB cf. CA 57, 1232a. Rats received 720 r. of x-radiation, intensity 80 r./min., after intraperitoneal injection of zymozan (I) with or without N'-phenyl-2-thiophenecarboxamidine (II). Treatment with I reduced radiation resistance in presence or absence of II. Symptoms of radiation disease appeared sooner and mortality rate was higher in animal receiving only I. This result is ascribed to the decreased serum properdin level assocd. with I.
IT **3737-39-1**, 2-Thiophenecarboxamidine, N-phenyl-
(in radiation-damage prevention)
RN 3737-39-1 HCAPLUS
CN 2-Thiophenecarboximidamide, N-phenyl- (9CI) (CA INDEX NAME)



L5 ANSWER 22 OF 23 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1962:412276 HCAPLUS
DOCUMENT NUMBER: 57:12276
ORIGINAL REFERENCE NO.: 57:2546i,2547a-b
TITLE: Changes in the peripheral blood caused by acute irradiation in albino rats protected by 2-thiophenecarboxylic acid N-phenylamidine
AUTHOR(S): Zorgrafov, D.; Baev, I.
SOURCE: Khirurgiya (Sofia) (1961), 14, 1109-12
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable
AB Two groups of albino rats were irradiated with 600 r.; one was a control and the other was injected with 5 mg./100 g. 1% HOAc soln. of the oraldine at pH 5. The protected group showed a greater decrease and quicker restoration of the erythrocytes and platelets. It is believed that the action of the chemoprotector is through a blocking of the early physiochem. reactions caused by radiation and not by protecting the systems regulating the regenerative processes.
IT **3737-39-1**, 2-Thiophenecarboxamidine, N-phenyl-
(in protection against blood changes from radiation)

RN 3737-39-1 HCAPLUS
CN 2-Thiophenecarboximidamide, N-phenyl- (9CI) (CA INDEX NAME)

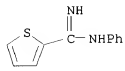


L5 ANSWER 23 OF 23 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1962:40228 HCAPLUS
DOCUMENT NUMBER: 56:40228
ORIGINAL REFERENCE NO.: 56:7664a-c
TITLE: Radioprotective effect of the N-phenylamidine of 2-thiophenecarboxylic acid depending on the dose used
AUTHOR(S): Nikolov, I.; Baev, I.; Robev, S.
SOURCE: Compt. Rend. Acad. Bulgare Sci. (1961), 14, 551-4
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Three of 4 groups of white rats, each consisting of 40 males and 40 females, were injected intraperitoneally 5-8 min. before irradiation with N-phenylamidine of 2-thiophenecarboxylic acid (I) in doses of 36, 48, and 60 mg. of I/kg.; the 4th group served as control with no I. All 4 groups were x-irradiated with 720 r. The radioprotective effect of I began to be manifest at doses of the order of 60 mg./kg. Below these doses there was a sharp decline in the radioprotective capacities of I. The percentage of survivals in the group 4 showed no sex difference. In the 2 lower dosage groups the curves of survivals (percentage of survivals vs. time) were the same for male and female rats. At 60 mg./kg. the percentage of survivals among the female animals was 60, while that among the males was 35. In the protected animals bodily exhaustion, the hemorrhagic syndrome, and diarrhea were expressed to a lesser degree and were completely absent in certain cases. The difference between the protected male and female rats indicates a possible significance of female sex hormones.

IT **3737-39-1**, 2-Thiophenecarboxamidine, N-phenyl-
(in radiation-damage prevention, dose in relation to)

RN 3737-39-1 HCAPLUS
CN 2-Thiophenecarboximidamide, N-phenyl- (9CI) (CA INDEX NAME)



CA Plus - for Compd A or B combined with Heat Stress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=> d que stat l14
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L3             1 SEA FILE=REGISTRY ABB=ON  7516-48-5/RN
L5            23 SEA FILE=HCAPLUS ABB=ON  (L1 OR PHENYL?(W)2(W)?THIOPHENECARBOXI
                 MID? OR ?PHENYL2THIOPHENECARBOXIMID?)
L6          3038 SEA FILE=HCAPLUS ABB=ON  (L3 OR ?LIPOIC?(W)?ACID? OR ?OCTANOIC?
                 (W)?ACID?(3A)(?DIMERCAPTO? OR DI(W)?MERCAPTO?))
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L9             1 SEA FILE=REGISTRY ABB=ON  MPTP/CN
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L11            1 SEA FILE=REGISTRY ABB=ON  DOPAMINE/CN
L12           53 SEA FILE=HCAPLUS ABB=ON  L8 AND (L11 OR ?DOPAMIN? OR ?METABOL?(
                 W)?ANTIOXID? OR ?SYNTHAS?(W)?INHIBIT?)
L13           28 SEA FILE=HCAPLUS ABB=ON  L12 AND (?FALL? OR ?REDUC? OR
                 ?MINIMIZ? OR ?LESS? OR ?DROP?)
L14           29 SEA FILE=HCAPLUS ABB=ON  L10 OR L13

=> d l14 ibib abs hitstr 1-29

L14  ANSWER 1 OF 29  HCAPLUS  COPYRIGHT 2003 ACS
ACCESSION NUMBER:         2002:922003  HCAPLUS
DOCUMENT NUMBER:          137:363100
TITLE:                    Determining the effect of compounds on the ability of
                          a subject to control their weight and compositions to
                          reduce the effect of such compounds
INVENTOR(S):              Buchanan-Baillie-Hamilton, Paula Frances; Peck, Julian
                          Claude
PATENT ASSIGNEE(S):       UK
SOURCE:                   Brit. UK Pat. Appl., 89 pp.
                          CODEN: BAXXDU
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.        KIND  DATE          APPLICATION NO.  DATE
     ---------------   ----  --------      ---------------  --------
     GB 2370504         A1   20020703      GB 2001-17052    20010712
PRIORITY APPLN. INFO.:                    GB 2000-19327    A  20000808
AB   A method of detg. the extent of the effect of a target compd. on the
     ability of a test subject to control their wt.  The method comprises the
     steps of detg. the degree or severity by which the compd. affects each of
     a plurality of wt. controlling systems present in the subject, detg. the
     persistence of the compd. in the subject and calcg. the effect as a
     function of these values.  The effect of target compds. including
     pesticides, environmental pollutants, org. solvents and heavy metals may
     be detd.  Wt. controlling systems that may be considered include the
     hormonal system, metab. and muscular activity.  A method of detg. the
     effect of an item on the ability of a subject to control their wt.
     comprises detg. the amt. in the item of a plurality of target compds.
     which effect the ability of the subject to control their wt.  A method of
     detg. the extent to which a subject has had their ability to control their
     wt. inhibited comprises detg. the amt. in the subject of a plurality of
     compds. which have an effect on the ability of the subject to control
     their wt.  Compns. to reduce the effect of one or more target
     compds. present in a subject which effect the ability of the subject to
     control their wt. comprise one or more micronutrients or target compd.
     absorbants which reduce the level of and/or counteract the
     effect of the target compds.  The compns. may be used in the treatment of
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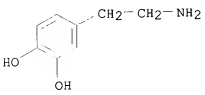
obesity.
IT **51-61-6**, **Dopamine**, biological studies
RL: BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(wt. controlling systems detn. with; detg. the effect of compds. on ability of a subject to control their body wt. and compns. to **reduce** the effect of such compds. in relation to obesity treatment)
RN 51-61-6 HCAPLUS
CN 1,2-Benzenediol, 4-(2-aminoethyl)- (9CI) (CA INDEX NAME)



L14 ANSWER 2 OF 29 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:803929 HCAPLUS
TITLE: Effect of DL-.alpha.-**lipoic acid** on the status of lipid peroxidation and protein oxidation in various brain regions of aged rats
AUTHOR(S): Arivazhagan, Palaniappan; Thilakavathy, Thangaswamy; Ramanathan, Kadirvel; Kumaran, Sundaram; Panneerselvam, Chinnakkannu
CORPORATE SOURCE: Institute of Basic Medical Sciences, Department of Medical Biochemistry, University of Madras, Taramani, Chennai, 600 113, India
SOURCE: Journal of Nutritional Biochemistry (2002), 13(10), 619-624
CODEN: JNBIEL; ISSN: 0955-2863
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Free radicals have been implicated in the development of many acute and chronic diseases and in conditions involving brain or neurol. tissue. The primary genetic material is subjected to damage by endogenous and exogenous agents, which may lead to instability and transcriptional infidelity. In the present study, we evaluated the protective effect of DL-.alpha.-**lipoic acid**, a **metabolic antioxidant** on lipid peroxidn., protein carbonyl content in various brain regions of aged rats when compared to brain regions of young rats. DL-.alpha.-**lipoic acid** was administered i.p. (100mg/kg body wt./day) to exptl. rats. Nucleic acid and protein content were low whereas thiobarbituric acid reactive substances and protein carbonyl content (markers of free radical damage) were high in cortex, striatum, hippocampus and hypothalamus followed by cerebellum of aged rat brain. Lipoate administration for 14 days in aged rats increased the levels of nucleic acid and protein and **reduced** lipid peroxidn. and protein oxidn. These results demonstrate that **lipoic acid** is a potent antioxidant for neuronal cells against age assocd. oxidative damage.
REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 3 OF 29 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2002:658744 HCAPLUS
DOCUMENT NUMBER: 137:190772
TITLE: Method and compositions containing amino sugars and nitric oxide scavengers for treating arthritis
INVENTOR(S): Petrus, Edward J.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 7 pp., Cont.-in-part of U.S. 6,346,519.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002119952	A1	20020829	US 2002-68249	20020205
US 6346519	B1	20020212	US 1999-350380	19990708
PRIORITY APPLN. INFO.:			US 1998-149241 B2	19980909
			US 1999-350380 A2	19990708

AB This invention relates to the compns. and method of treating and preventing arthritis, repairing of articular joint surfaces and the relief of symptoms assocd. with arthritis. The compn. comprises bio-affecting agents to **reduce** nitric oxide prodn. and increase **chondroprotective** agents. The preferred compn. comprises; nitric oxide **synthase inhibitors**, nitric oxide scavengers, and amino sugars. Nitric oxide **synthase inhibitors** and nitric oxide scavengers **reduce** the level of nitric oxide, the free radical responsible for the degrdn. of articular cartilage. Amino sugars are the building blocks of articular cartilage and have anti-inflammatory actions. A 60-yr old male with diagnosed osteoarthritis of both knees was started on a compn. of glucosamine sulfate 500 mg, niacinamide 50 mg, resveratrol 1 mg, methylsulfonylmethane 25 mg, bromelain 40 mg, papain 50 mg and zinc sulfate 5 mg, taken three times a day for 6 mo. After 2 wk, knee pain was markedly **reduced** and sensitivity over the patella was minimal. Full range of motion was achieved after 3 wk. After 1 mo the dosage was **reduced** to twice a day and maintained for the duration of the study.

L14 ANSWER 4 OF 29 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:114062 HCAPLUS
DOCUMENT NUMBER: 136:161358
TITLE: Method and composition using a nitric oxide **synthase inhibitor** and an amino sugar for treating arthritis
INVENTOR(S): Petrus, Edward J.
PATENT ASSIGNEE(S): Advanced Medical Instruments, USA
SOURCE: U.S., 6 pp., Cont.-in-part of U.S. Ser. No. 149,241, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6346519	B1	20020212	US 1999-350380	19990708
US 2002119952	A1	20020829	US 2002-68249	20020205
PRIORITY APPLN. INFO.:			US 1998-149241 B2	19980909

US 1999-350380 A2 19990708

AB A compn. and method are provided for treating arthritis, repairing of articular joint surfaces, and the relief of symptoms assocd. with arthritis. The compn. comprises a nitric oxide **synthase inhibitor** and amino sugars. The nitric oxide **synthase inhibitor reduces** the level of nitric oxide, the free radical believed responsible for the degrdn. of articular cartilage. Amino sugars are the building blocks of articular cartilage and have antiinflammatory actions.

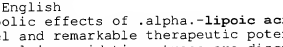
REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 5 OF 29 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:732805 HCAPLUS
DOCUMENT NUMBER: 136:182956
TITLE: .alpha.-**Lipoic acid**: the **metabolic antioxidant**
AUTHOR(S): Lodge, John K.; Packer, Lester
CORPORATE SOURCE: Department of Molecular and Cell Biology, University of California, Berkeley, CA, USA
SOURCE: Nutrition and Immunology (2000), 97-106. Editor(s): Gershwin, M. Eric; German, J. Bruce; Keen, Carl L. Humana Press Inc.: Totowa, N. J.
CODEN: 69BXBA
DOCUMENT TYPE: Conference; General Review
LANGUAGE: English

AB A review. The metabolic effects of .alpha.-**lipoic acid** at the cellular level and remarkable therapeutic potential of lipoate in various disorders involving oxidative stress are discussed. The **lipoic acid/dihydrolipoic acid** (DHLA) couple has been described as a universal antioxidant. Both compds. can scavenge a wide variety of reactive oxygen species and have metal-chelating properties. The .alpha.-**lipoic acid** is rapidly absorbed from dietary supplements, distributed to body tissues, and taken up by the cells, where it is **reduced** to DHLA. Intracellular glutathione levels are also increased markedly after dietary **lipoic acid** supplementation, thus **lipoic acid** can affect cellular redox status.

IT **462-20-4**, **Dihydrolipoic acid**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(dietary .alpha.-**lipoic acid** and its antioxidant nutritional biochem.)

RN 462-20-4 HCAPLUS
CN Octanoic acid, 6,8-dimercapto- (8CI, 9CI) (CA INDEX NAME)



REFERENCE COUNT: 85 THERE ARE 85 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 6 OF 29 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:693317 HCAPLUS
DOCUMENT NUMBER: 135:257089
TITLE: Preparation and use of novel **lipoic acid** heterocyclic or benzene derivatives as medicines

INVENTOR(S): Harnett, Jeremiah; Auguet, Michel
PATENT ASSIGNEE(S): Societe de Conseils de Recherches et d'Applications Scientifiques (S.C.R.A.S.), Fr.
SOURCE: PCT Int. Appl., 49 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001068643	A2	20010920	WO 2001-FR764	20010315
WO 2001068643	A3	20020606		
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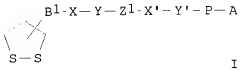
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
FR 2806409	A1	20010921	FR 2000-3355	20000316
FR 2806409	B1	20020419		
EP 1265891	A2	20021218	EP 2001-917143	20010315
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				

PRIORITY APPLN. INFO.:
FR 2000-3355 A 20000316
FR 2000-12007 A 20000921
WO 2001-FR764 W 20010315

OTHER SOURCE(S): CASREACT 135:257089; MARPAT 135:257089
GI



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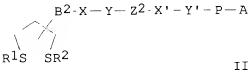

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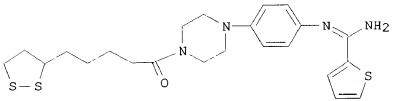


III

AB The invention concerns novel heterocyclic or benzene derivs., e.g., I [A = N:C(A')NH2; A' = linear or branched C1-6-alkyl, 5-6 membered aryl or heterocycle; B1, B2 = (CH2)n; P = (CH2)g, R6-substituted phenylene; XY = O(CH2)r, NR3(CH2)r, CO(CH2)r, CONR3(CH2)2, NR4CO(CH2)r, NR3CONR4(CH2)r; X'Y' = (CH2)r, (CH2)rO(CH2)r, (CH2)rNR3(CH2)r,(CH2)rCO(CH2)r, (CH2)rCONR3(CH2)r, (CH2)rNR4CO(CH2)r,(CH2)NR3rCONR4(CH2)r; Z1, Z2 = 5-6 membered arom. heterocyclic, 4-7 non-arom. heterocyclic; Ph, C6H5R5; R1, R2 = H, linear or branched C1-6-alkyl; R3, R4 = H, alkyl, alkoxycarbonyl, aralkoxycarbonyl; R5 = H, linear or branched C1-6-alkyl, (CH2)m-Q; Q = H, OH, CN, NH2, alkoxy, (di)alkylamino; R6 = linear or branched C1-6-alkyl, (CH2)n-Q'; Q' = halogen, CF3, OH, NH2, CN, alkoxycarbonyl, aralkoxycarbonyl, alkoxy, alkylthio, (di)alkylamino; n = 0 - 6; g = 0 - 6; r = 0 - 6; m = 0 - 6] and II, or their pharmaceutically acceptable salts, comprising a lateral chain derived from **lipoic acid**, having an activity inhibiting NO-synthase enzymes producing NO nitrogen monoxide and/or are agents enabling regeneration of antioxidants or entities trapping reactive oxygen species (ROS) and intervening more generally in the redox status of thiol groups, methods for prepg. them, pharmaceutical compns. contg. them and their therapeutic use, particularly their use as NO-**synthase inhibitors** and/or as agents involved more generally in the redox status of thiol groups. Thus, thiophenecarboximidamide III.cntdot.HCl was prepd. from DL-thioctic acid, HS(CH2)2CH(SH)(CH2)4CO2H, via amidation with N-(p-nitrophenyl)piperazine, nitro group **redn.** and condensation with S-methyl-2-thiophenethiocarboximide hydroiodide. III.cntdot.HCl was tested for inhibition of NO synthase from rat cerebellum (CI50 = 4.5 .mu.M) and for its effect on oxidative stress induced by glutamate on HT-22 cell cultures (CE50 = 4 .mu.M).

L14 ANSWER 7 OF 29 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:338385 HCAPLUS
DOCUMENT NUMBER: 134:348264
TITLE: Product comprising at least a NO **synthase inhibiting** substance associated with at least a phospholipase A2 inhibiting substance
INVENTOR(S): Auguet, Michel; Chabrier de Lassauniere, Pierre-Etienne
PATENT ASSIGNEE(S): Societe de Conseils de Recherches et d'Applications Scientifiques (S.C.R.A.S.), Fr.
SOURCE: PCT Int. Appl., 37 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001032216	A2	20010510	WO 2000-FR3066	20001103
WO 2001032216	A3	20020328		

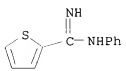
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,

BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
FR 2800615 A1 20010511 FR 1999-13859 19991105
FR 2800615 B1 20020503
EP 1233786 A2 20020828 EP 2000-974645 20001103
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR
PRIORITY APPLN. INFO.: FR 1999-13859 A 19991105
WO 2000-FR3066 W 20001103

AB The invention concerns a product comprising at least a NO **synthase inhibiting** substance assocd. with at least a phospholipase A2 inhibiting substance, sep. or combined, for simultaneous therapeutic use, sep. or spread over time for treating pathologies in which nitrogen monoxide and/or phosplipases A2 are involved. The invention also concerns a pharmaceutical compn. comprising, as active principle, at least a NO **synthase inhibiting** substance and at least a phospholipase A2 inhibiting substance, and optionally a pharmaceutically acceptable carrier. Administration of 25 mg 7-nitroindazole/kg and 30 mg mepacrine/kg in rats had synergistic effect and **reduced** the carrageenin-induced inflammation significantly.

IT **3737-39-1**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(product comprising at least NO **synthase inhibiting** substance assocd. with at least phospholipase A2 inhibiting substance)

RN 3737-39-1 HCAPLUS
CN 2-Thiophenecarboximidamide, N-phenyl- (9CI) (CA INDEX NAME)



L14 ANSWER 8 OF 29 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:328844 HCAPLUS
DOCUMENT NUMBER: 135:117135
TITLE: Effect of .alpha.-**lipoic acid** on apoptosis of PC12 cell induced by 6-**hydroxydopamine**
AUTHOR(S): Yuan, Chonggang; He, Ling; Xue, Xiaolin; Shi, Yingtang; Bi, Xiuhua
CORPORATE SOURCE: Department of Biology, East China Normal University, Shanghai, 200062, Peop. Rep. China
SOURCE: Shiyan Shengwu Xuebao (2001), 34(1), 65-70
CODEN: SYSWAE; ISSN: 0001-5334
PUBLISHER: Shanghai Kexue Jishu Chubanshe
DOCUMENT TYPE: Journal
LANGUAGE: Chinese

AB The effects of .alpha.-**lipoic acid** on apoptosis of PC12 cell induced by 6-**hydroxydopamine** (6-OHDA) were studied. The results from MTT method showed that 6-OHDA decreased the cell survival rate significantly. Through TUNEL (TdT-mediated dUTP-biotin nick end labeling) and Flow cytometer (FCM) detection, it was found that 6-OHDA triggered cell apoptosis and induced necrosis. It was confirmed by the different percentage of cell survival rate and apoptosis concluded from FXM and MTT. The .alpha.-**lipoic acid** was used as

antioxidant to protect the cell from injury of 6-OHDA. The result indicated that the .alpha.-**lipoic acid** could partly prevent apoptosis induced by 6-OHDA but fail to prevent necrosis since it could decrease the apoptotic cell from 20.09 to 3.09%, just as increased cell survival rate from 56.8 to 72.6% but could not reach the normal level showed by MTT assay. Biochem. approach showed the cell's antioxidant ability especial for SOD activity and GSH content increased after the treatment of the .alpha.-**lipoic acid**. The data suggested that the .alpha.-**lipoic acid** might protect PC12 cells from apoptosis induced by 6-OHDA through the antioxidant path.

L14 ANSWER 9 OF 29 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:208083 HCAPLUS
DOCUMENT NUMBER: 134:242632
TITLE: Method for modulating the metabolism of nitrogen oxides, compositions therefor (and variants) and method for acting on a patient's organism necessitating the metabolism of nitrogen oxides to be corrected
INVENTOR(S): Beda, Nataliya Vladimirovna; Gordin, Vladimir Alexandrovich; Nedospasov, Andrei Arturovich; Rafikov, Ruslan Robertovich; Rafikova, Olga Valerievna; Suntsova, Tatiyana Pavlovna
PATENT ASSIGNEE(S): Institut Molekulyarnoi Genetiki Rossiiskoi Akademii Nauk (IMG RAN), Russia
SOURCE: PCT Int. Appl., 38 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Russian
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001019341	A1	20010322	WO 2000-RU362	20000911
W: CA, JP, MX, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
RU 2161122	C1	20001227	RU 1999-119464	19990910
EP 1214933	A1	20020619	EP 2000-963185	20000911
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY				

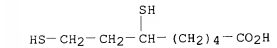
PRIORITY APPLN. INFO.: RU 1999-119464 A 19990910
WO 2000-RU362 W 20000911

AB The invention relates to a process of modification of the nitrogen oxides metab. by means of modification of the micellar catalysis parameters of NO oxidn. According to the invention, the no. of phases and/or the vol. ratio of the phases and/or the coeffs. of distribution of NO and O2 between the phases are modified. The no. of phases is modified by using perfluorocarbons, haloid derivs. thereof and perfluoralkylamines with a high coeff. of distribution of NO and O2, which are used as a **hydrophobic** phase for micellar anal. The invention also relates to compns. used to vary the output of nitrite, nitrate, nitrosothiols and other oxidn. products, whereby said compns. include emulsions of perfluororg. compds., catalysts and inhibitors of excessive nitrosation, **reducers**, free radical scavengers and nitrosation targets which modify the balance of the nitrosated biogenic compds. The inventive methods for acting on a patient's body include using such compns. together with variations in temp. and moisture and with traditional drugs. Independent claims in this invention also relate to the use of the known

blood replacement substances contg. perfluorated compds. and use of the steam bath or the sauna in order to accelerate NO oxidn.

IT **462-20-4, Dihydrolipoic acid**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(nitrosation of; perfluoro compds. for modulating the metab. of nitrogen oxides)

RN 462-20-4 HCAPLUS
CN Octanoic acid, 6,8-dimercapto- (8CI, 9CI) (CA INDEX NAME)



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 10 OF 29 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:616235 HCAPLUS
DOCUMENT NUMBER: 134:127858
TITLE: Radiolabeled neuronal nitric oxide **synthase inhibitors**: synthesis, in vivo evaluation, and primate PET studies
AUTHOR(S): Pomper, Martin G.; Musachio, John L.; Scheffel, Ursula; Macdonald, James E.; McCarthy, Dennis J.; Reif, David W.; Villemagne, Victor L.; Yokoi, Fuji; Dannals, Robert F.; Wong, Dean F.
CORPORATE SOURCE: Department of Radiology, Johns Hopkins University School of Medicine, Baltimore, MD, 21287-2182, USA
SOURCE: Journal of Nuclear Medicine (2000), 41(8), 1417-1425
CODEN: JNMEAQ; ISSN: 0161-5505
PUBLISHER: Society of Nuclear Medicine, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The objectives of this study were to synthesize neuronal nitric oxide synthase (NOS-I)-selective imaging agents based on the 2 potent, selective inhibitors AR-R 17443 [N-(4-((2-((phenylmethyl)(methyl)- amino)ethyl) **phenyl**)**-2-thiophenecarboximidamide**)] and AR-R 18512 [(N-(2-methyl-1,2,3,4-tetrahydroisoquinoline-7-yl)-2-thiophenecarboximidamide)] in positron-emitting form and to evaluate regional brain uptake in rodents and primates. Methods: [11C]AR-R 17443 and [11C]AR-R 18512 were produced by N-alkylation of the corresponding desmethyl precursors using [11C]iodomethane. Regional brain uptake of [11C]AR-R 17443 and [11C]AR-R 18512 was assayed in rats and NOS-I knockout mice, and PET was performed in baboons. Tracer kinetic modeling used a 2-compartment plasma and brain tissue model. Results: Yields of [11C]AR-R 17443 and [11C]AR-R 18512 ranged from 8% to 16% at the end of synthesis, with specific activities of 50-178 GBq/.mu.mol (1350-4800 Ci/mmol) at the end of synthesis. In rat cerebellum and cortex at 30 min after injection, [11C]AR-R 17443 showed 1.01 .+-. 0.01 and 1.63 .+-. 0.12 percentage injected dose per g (%ID/g) uptake, resp., whereas [11C]AR-R 18512 showed 0.88 .+-. 0.01 and 1.30 .+-. 0.07 %ID/g uptake, resp. Attempts to block tracer uptake by pretreatment with the NOS-I-selective inhibitor 7-nitroindazole or the corresponding unlabeled inhibitor (or desmethyl precursor to AR-R 17443 of similar potency) were unsuccessful. A small but significant (20%) decrease in cerebellar uptake of [11C]AR-R 18512 was present in NOS-I knockout mice compared with control mice. PET of [11C]AR-R 18512 in baboons with concurrent regional cerebral blood flow

(rCBF) detn. before and after administration of blocker showed dose-related decreases in cerebellar uptake that were greater than or equal to decreases in rCBF. Plasma metabolites accounted for 27% of total activity at 30 min after injection. Kinetic modeling of binding potentials revealed a distribution vol. of 334 in cerebral blood that **dropped** 51% after blocker administration. Conclusion: Rodent studies for [11C]AR-R 17443 and [11C]AR-R 18512 showed little evidence of specific NOS-I binding. In baboons, we detected a higher uptake of [11C]AR-R 18512 in the cerebellum than in the cortex (approx. 5%, accounting for decreased rCBF because of blockade), indicating minimal specific binding. Analogs of higher affinity are likely required if this class of agents is to prove viable for PET.

REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 11 OF 29 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:490358 HCAPLUS
DOCUMENT NUMBER: 133:202864
TITLE: ARL 17477, a selective nitric oxide **synthase inhibitor**, with neuroprotective effects in animal models of global and focal cerebral ischemia
AUTHOR(S): O'Neill, M. J.; Murray, T. K.; McCarty, D. R.; Hicks, C. A.; Dell, C. P.; Patrick, K. E.; Ward, M. A.; Osborne, D. J.; Wiernicki, T. R.; Roman, C. R.; Lodge, D.; Fleisch, J. H.; Singh, J.
CORPORATE SOURCE: Lilly Research Centre, Eli Lilly and Co. Ltd., Windlesham, Surrey, GU20 6PH, UK
SOURCE: Brain Research (2000), 871(2), 234-244
CODEN: BRREAP; ISSN: 0006-8993
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In the present studies, we have evaluated the effects of N-[4-(2-{[(3-Chlorophenyl)methyl]amino}ethyl)**phenyl**]-2**-thiophenecarboximidamide** dihydrochloride (ARL 17477) on recombinant human neuronal NOS (nNOS) and endothelial NOS (eNOS). We then carried out pharmacokinetic studies and measured cortical nitric oxide synthase (NOS) inhibition to det. that the compd. crossed the blood brain barrier. Finally, the compd. was evaluated in a model of global ischemia in the gerbil and two models of transient focal ischemia in the rat. The IC50 values for ARL 17477 on human recombinant human nNOS and eNOS were 1 and 17 .mu.M, resp. ARL 17477 (50 mg/kg i.p.) produced a significant **redn.** in the ischemia-induced hippocampal damage following global ischemia when administered immediately post-occlusion, but failed to protect when administration was delayed until 30 min post-occlusion. In the endothelin-1 model of focal ischemia, ARL 17477 (1 mg/kg i.v.) significantly attenuated the infarct vol. when administered at either 0, 1 or 2 h post-endothelin-1 (P<0.05). In the intraluminal suture model, ARL 17477 at both 1 and 3 mg/kg i.v. failed to **reduce** the infarct vol. measured at 1, 3 or 7 days post-occlusion. These results demonstrate that ARL 17477 protects against global ischemia in gerbils and provides some **redn.** in infarct vol. following transient middle cerebral artery occlusion in rats, indicating that nNOS inhibition may be a useful treatment of ischemic conditions.

REFERENCE COUNT: 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 12 OF 29 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:161085 HCAPLUS
DOCUMENT NUMBER: 132:179851

TITLE: Antioxidant composition comprising acetyl L-carnitine and .alpha.-**lipoic acid**
INVENTOR(S): Cavazza, Claudio
PATENT ASSIGNEE(S): Sigma-Tau Healthscience S.P.A., Italy
SOURCE: PCT Int. Appl., 27 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000011968	A1	20000309	WO 1999-IT268	19990819
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
IT 1302307	B1	20000905	IT 1998-RM566	19980901
CA 2341973	AA	20000309	CA 1999-2341973	19990819
AU 9953871	A1	20000321	AU 1999-53871	19990819
BR 9913288	A	20010522	BR 1999-13288	19990819
EP 1112005	A1	20010704	EP 1999-939612	19990819
EP 1112005	B1	20021127		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
EE 200100113	A	20020617	EE 2001-200100113	19990819
JP 2002523435	T2	20020730	JP 2000-567099	19990819
AT 228312	E	20021215	AT 1999-939612	19990819
NO 2001000954	A	20010425	NO 2001-954	20010226
US 6365622	B1	20020402	US 2001-786153	20010312

PRIORITY APPLN. INFO.: IT 1998-RM566 A 19980901
WO 1999-IT268 W 19990819

AB A compn. is disclosed which comprises as characterizing active ingredients acetyl L-carnitine and .alpha.-**lipoic acid**, for the prevention and/or therapeutic treatment of various alterations and pathol. states induced by free radicals, that may take the form of a dietary supplement, dietetic support or of an actual medicine.

REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 13 OF 29 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:1000 HCAPLUS
DOCUMENT NUMBER: 132:274174
TITLE: .alpha.-**lipoic acid** prevents 3,4-methylenedioxymethamphetamine (MDMA)-induced neurotoxicity
AUTHOR(S): Aguirre, Norberto; Barrionuevo, Meritxell; Ramirez, Maria J.; Del Rio, Joaquin; Lasheras, Berta
CORPORATE SOURCE: Department of Pharmacology, School of Medicine, University of Navarra, Pamplona, 31008, Spain
SOURCE: NeuroReport (1999), 10(17), 3675-3680
CODEN: NERPEZ; ISSN: 0959-4965
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal

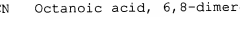
LANGUAGE: English
AB A single administration of 3,4-methylenedioxymethamphetamine (MDMA, 20 mg/kg, i.p.) induced significant hyperthermia in rats and **reduced** 5-hydroxytryptamine (5-HT) content and [3H]paroxetine-labeled 5-HT transporter d. in the frontal cortex, striatum, and hippocampus by 40-60% 1 wk later. MDMA treatment also increased glial fibrillary acidic protein (GFAP) immunoreactivity in the hippocampus. Repeated administration of the **metabolic antioxidant** .alpha.-**lipoic acid** (100 mg/kg, i.p., b.i.d. for 2 consecutive days) 30 min prior to MDMA did not prevent the acute hyperthermia induced by the drug; however, it fully prevented the serotonergic deficits and the changes in the glial response induced by MDMA. These results further support the hypothesis that free radical formation is responsible for MDMA-induced neurotoxicity.
REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 14 OF 29 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:600734 HCAPLUS
DOCUMENT NUMBER: 132:116925
TITLE: **Lipoic acid** and **dihydrolipoic acid** as **metabolic antioxidants**
AUTHOR(S): Matsugo, Seiichi
CORPORATE SOURCE: Department of Chemical & Biochemical Engineering, Faculty of Engineering, Toyama University, Toyama, 930-8555, Japan
SOURCE: Furi Rajikaru no Rinsho (1998), 13, 79-84
CODEN: FRRIFI
PUBLISHER: Nihon Igakukan
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Japanese
AB A review with 41 refs. **Lipoic acid** was first isolated by Reed and coworkers in 1951. As lipoamide, it is a cofactor in the multienzyme complexes which catalyze the oxidative decarboxylation of .alpha.-keto acids such as .alpha.-ketoglutarate and pyruvate. In addn. to this pivotal role in energy metab., the accumulating results demonstrate the strong antioxidant activity of **lipoic acid** and its **reduced** form **dihydrolipoic acid**. **Lipoic acid** is smoothly converted to its **reduced** form, **dihydrolipoic acid** in vivo by receiving two electrons by the action of NADH. **Dihydrolipoic acid** is well characterized by the two thiol groups, which play the significant role in the antioxidant activity. **Lipoic acid** is characterized by the strained 1,2-dithiolane ring chromophore. In this paper, the crit. evaluation of the antioxidant activity of **lipoic acid** and **dihydrolipoic acid** was described from the mol. standpoint of view.
IT **462-20-4, Dihydrolipoic acid**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(**lipoic acid** and **dihydrolipoic acid** as **metabolic antioxidants**)
RN 462-20-4 HCAPLUS
CN Octanoic acid, 6,8-dimercapto- (8CI, 9CI) (CA INDEX NAME)

L14 ANSWER 15 OF 29 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:274427 HCAPLUS
DOCUMENT NUMBER: 131:57249
TITLE: Hypoxia induces permeability in brain microvessel endothelial cells via VEGF and NO
AUTHOR(S): Fischer, Silvia; Clauss, Matthias; Wiesnet, Marion; Renz, Dieter; Schaper, Wolfgangrd; Karliczek, Gerhard F.
CORPORATE SOURCE: Departments of Anesthesiology and Intensive Care, Max Planck Institute for Physiological and Clinical Research, Bad Nauheim, 61231, Germany
SOURCE: American Journal of Physiology (1999), 276(4, Pt. 1), C812-C820
CODEN: AJPHAP; ISSN: 0002-9513
PUBLISHER: American Physiological Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In this study, an in vitro model of the blood-brain barrier, consisting of porcine brain-derived microvascular endothelial cells (BMEC), was used to evaluate the mechanism of hypoxia-induced hyperpermeability. We show that hypoxia-induced permeability in BMEC was completely abolished by a neutralizing antibody to vascular endothelial growth factor (VEGF). In contrast, under normoxic conditions, addn. of VEGF up to 100 ng/mL did not alter monolayer barrier function. Treatment with either hypoxia or VEGF under normoxic conditions induced a twofold increase in VEGF binding sites and VEGF receptor 1 (Flt-1) mRNA expression in BMEC. Hypoxia-induced permeability also was prevented by the nitric oxide (NO) **synthase inhibitor** NG-monomethyl-L-arginine, suggesting that NO is involved in hypoxia-induced permeability changes, which was confirmed by measurements of the cGMP level. During normoxia, treatment with VEGF (5 ng/mL) increased permeability as well as cGMP content in the presence of several antioxidants. These results suggest that hypoxia-induced permeability in vitro is mediated by the VEGF/VEGF receptor system in an autocrine manner and is essentially dependent on **reducing** conditions stabilizing the second messenger NO as the mediator of changes in barrier function of BMEC.
REFERENCE COUNT: 71 THERE ARE 71 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 16 OF 29 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:164533 HCAPLUS
DOCUMENT NUMBER: 131:13938
TITLE: Attenuation of aminoglycoside-induced cochlea damage with the **metabolic antioxidant** .alpha.-**lipoic acid**
AUTHOR(S): Conlon, Brendan J.; Aran, Jean-Marie; Erre, Jean-Paul; Smith, David W.
CORPORATE SOURCE: The Hearing Research Laboratories, Division of Otolaryngology-Head and Neck Surgery, Duke University Medical Center, Durham, NC, 27710, USA
SOURCE: Hearing Research (1999), 128(1-2), 40-44
CODEN: HERED3; ISSN: 0378-5955
PUBLISHER: Elsevier Science B.V.

DOCUMENT TYPE: Journal
LANGUAGE: English
AB Free radical generation is increasingly implicated in a variety of pathol. processes, including drug toxicity. Recently, a no. of studies have demonstrated the ability of gentamicin to facilitate the generation of radical species both in vivo and in vitro, which suggests that this process plays an important role in aminoglycoside-induced ototoxicity. Free radical scavengers are compds. capable of inactivating free radicals, thereby attenuating their tissue damaging capacity. In this study we have detd. the ability of the powerful free radical scavenger .alpha.-**lipoic acid** (100 mg/kg/day) to attenuate the cochlear damage induced by a highly ototoxic regimen of the aminoglycoside amikacin (450 mg/kg/day, i.m.). Expts. were carried out on pigmented guinea pigs initially weighing 200-250 g. Changes in cochlear function were characterized as shifts in compd. action potential (CAP) thresholds, estd. every 5 days, by use of chronic indwelling electrodes implanted at the round window, vertex, and contralateral mastoid. Results showed that animals receiving .alpha.-**lipoic acid** in combination with amikacin demonstrated a signif icantly **less** severe elevation in CAP thresholds compared with animals receiving amikacin alone ($P<0.001$; t-test). These results provide further evidence of the recently reported intrinsic role of free radical generation in aminoglycoside ototoxicity, and highlight a potential clin. therapeutic use of .alpha.-**lipoic acid** in the management of patients undergoing aminoglycoside treatment.
IT **462-20-4**, **Dihydrolipoic acid**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(attenuation of aminoglycoside-induced cochlear damage with the **metabolic antioxidant** .alpha.-**lipoic acid**)
RN 462-20-4 HCAPLUS
CN Octanoic acid, 6,8-dimercapto- (8CI, 9CI) (CA INDEX NAME)



REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 17 OF 29 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:359923 HCAPLUS
DOCUMENT NUMBER: 129:147032
TITLE: .alpha.-**Lipoic acid**: a **metabolic antioxidant** which regulates NF-.kappa.B signal transduction and protects against oxidative injury
AUTHOR(S): Packer, Lester
CORPORATE SOURCE: Department of Molecular and Cell Biology, University of California, Berkeley, CA, 94720-3200, USA
SOURCE: Drug Metabolism Reviews (1998), 30(2), 245-275
CODEN: DMTRAR; ISSN: 0360-2532
PUBLISHER: Marcel Dekker, Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 113 refs., on .alpha.-**lipoic acid**, with

resp. to history and biochem,; **redn**. of .alpha.-**lipoic acid**; free-radical scavenging; interactions with other antioxidants; effects on oxidant-induced injury; effects on NF-.kappa.B activation, and current models for intracellular glutathione up-regulation by .alpha.-**lipoic acid**.

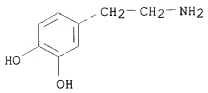
REFERENCE COUNT: 113 THERE ARE 113 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 18 OF 29 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:358046 HCAPLUS
DOCUMENT NUMBER: 129:64716
TITLE: Inactivation of glutathione **reductase** by the Cu(II)/H2O2 system: effect of thiols and catecholamines
AUTHOR(S): Gutierrez Correa, Jose; Stoppani, Andres O. M.
CORPORATE SOURCE: Cent. Investigachions Bioenergeticas (CONICET), Fac. Med., UBA, Buenos Aires, 1121, Argent.
SOURCE: Anales de la Asociacion Quimica Argentina (1997), 85(5-6), 217-230
CODEN: AAQAAE; ISSN: 0365-0375
PUBLISHER: Associacion Quimica Argentina
DOCUMENT TYPE: Journal
LANGUAGE: Spanish

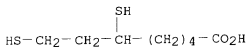
AB Yeast glutathione **reductase** (GR) was inactivated by the Cu-Fenton system (FS; Cu(II)/H2O2). Several monothiols namely cysteine, N-acetylcysteine, mercaptopropionylglycine and penicillamine increased GR inactivation by the Cu(II)/H2O2, the inactivation reaching max. values at about 0.20 mM thiol. Glutathione (GSH), dithiothreitol, **dihydrolipoic acid** and Captopril produced similar effects at concns. up to about 0.2 mM, but higher concns. were **less** effective, specially during short-time incubations. Oxidized GSH (GSSG) and the disulfide trypanothione protected GR against Cu(II)/H2O2. Generally speaking, the effect of thiols on GR inactivation correlated with the latter compds. capability for generating hydroxyl radicals, in the presence of Cu(II)/H2O2. Cu(II)-complexing agents (EDTA and DETAPAC) at adequate concns. prevented GR inactivation by Cu(II)/H2O2. The Cu(II)/RSH systems (H2O2 omitted) also inactivated GR but, to a **lesser** degree than the corresponding Cu(II)/H2O/RSH systems. Superoxide dismutase and catalase prevented GR inactivation by the Cu(II)/RSH systems thus proving the role of superoxide radical and H2O2, resp. Catecholamines (epinephrine- norepinephrine, **dopamine**, 6-**hydroxydopamine**, L-DOPA, DOPAC), pyrogallol and the dicatechol nordihydroguaiaretic acid enhanced, like thiols, GR inactivation by Cu(II)/H2O2,.cntdot. **lesser** effects were obsd. with the Cu(II)/catecolamines systems (H2O2 omitted). It is concluded that GR inactivation by the Cu(II)/H2O2/RSH systems depends on a chain of reaction producing HO- radicals. That chain involves copper ions, superoxide anions and H2O2. A similar reaction mechanism would operate with the Cu(II)/H2O2/catecholamine and related systems.

IT **51-61-6, Dopamine**, biological studies **462-20-4**, **Dihydrolipoic acid**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(inactivation of glutathione **reductase** by Cu(II)/H2O2 system: effect of thiols and catecholamines)

RN 51-61-6 HCAPLUS
CN 1,2-Benzenediol, 4-(2-aminoethyl)- (9CI) (CA INDEX NAME)



RN 462-20-4 HCAPLUS
CN Octanoic acid, 6,8-dimercapto- (8CI, 9CI) (CA INDEX NAME)



REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 19 OF 29 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:296966 HCAPLUS
DOCUMENT NUMBER: 129:39591
TITLE: Effects of the antioxidant .alpha.-**lipoic acid** on human umbilical vein endothelial cells infected with Rickettsia rickettsii
AUTHOR(S): Eremeeva, Marina E.; Silverman, David J.
CORPORATE SOURCE: School of Medicine, University of Maryland, Baltimore, Baltimore, MD, 21201, USA
SOURCE: Infection and Immunity (1998), 66(5), 2290-2299
CODEN: INFIBR; ISSN: 0019-9567
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Rickettsia rickettsii infection of endothelial cells is manifested in very distinctive changes in cell morphol., consisting of extensive dilatation of the membranes of the endoplasmic reticulum and outer nuclear envelope and blebbing of the plasma membrane, as seen by TEM (D. J. Silverman, Infect. Immun. 44:545-553, 1984). These changes in cellular architecture are thought to be due to oxidant-mediated cell injury, since their occurrence correlates with dramatic alterations in cellular metab., particularly with regard to antioxidant systems. In this study, it was shown that R. rickettsii infection of human umbilical vein endothelial cells resulted in a significant depletion of intracellular **reduced** glutathione (thiol) content at 72 and 96 h and decreased glutathione peroxidase activity at 72 h postinfection. Infected cells displayed a dramatic increase in the concn. of intracellular peroxides by 72 h. Supplementation of the cell culture medium with 100, 200, or 500 .mu.M .alpha.-**lipoic acid**, a **metabolic antioxidant**, after inoculation with R. rickettsii restored the intracellular levels of thiols and glutathione peroxidase and **reduced** the intracellular peroxide levels in infected cells. These effects were dose dependent. Treated infected monolayers maintained better viability at 96 h after inoculation with R. rickettsii than did untreated infected cells. Moreover, supplementation of the cell culture medium with 100 .mu.M .alpha.-**lipoic acid** for 72 h after infection prevented the occurrence of morphol. changes in the infected cells. The presence of 100 or 200 .mu.M .alpha.-**lipoic acid** did not influence rickettsial growth in endothelial cells, nor did it affect the ability of R. rickettsii to form lytic plaques in

Vero cells. Treatment with 500 .mu.M .alpha.-**lipoic acid** decreased by 50% both the no. and size of lytic plaques in Vero cells, and it also decreased the recovery of viable rickettsiae from endothelial cells. However, under all treatment conditions, a significant no. of rickettsiae could be detected microscopically. Furthermore, the rickettsiae apparently retained their capacity for intracellular movement, since they possessed long polymd. actin tails after 72 and 96 h of treatment **regardless** of the concn. of .alpha.-**lipoic acid** used. Since .alpha.-**lipoic acid** does not seem to exhibit direct antirickettsial activity except with long-term exposure at very high concns., the mechanism of its protective activity for endothelial cells infected with rickettsiae may involve complex changes in cellular metab. that only indirectly affect rickettsiae.

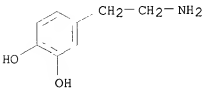
REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 20 OF 29 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:119426 HCAPLUS
DOCUMENT NUMBER: 128:149358
TITLE: Inhibitory effect of some biological compounds on catecholamines peroxidation
AUTHOR(S): Kruk, J.; Kladna, A.; Aboul-Enein, H. Y.; Kruk, I.
CORPORATE SOURCE: Department Human Ecology, Faculty Natural Sciences, University Szczecin, Szczecin, 71-065, Pol.
SOURCE: Toxicological and Environmental Chemistry (1998), 65(1-4), 135-144
CODEN: TECSDY; ISSN: 0277-2248
PUBLISHER: Gordon & Breach Science Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The inhibitory effect of biol. important compds. on catecholamines (adrenaline, noradrenaline, **dopamine**) peroxidn. with respect to prodn. of reactive O species, esp. hydroxyl radicals was investigated by chemiluminescence in presence of the Cu(II) + H2O2 system. Carnosine, myoglobin, cimetidine, methionine, captopril, .alpha.-**lipoic acid**, glutathione, were strongly effective as antioxidants.

IT **51-61-6, Dopamine**, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(biol. compds. inhibitory effect on catecholamines peroxidn. detd. by an Cu(II) + H2O2 system)

RN 51-61-6 HCAPLUS
CN 1,2-Benzenediol, 4-(2-aminoethyl)- (9CI) (CA INDEX NAME)



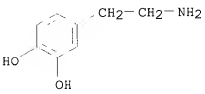
L14 ANSWER 21 OF 29 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:97187 HCAPLUS
DOCUMENT NUMBER: 128:267537
TITLE: Inactivation of yeast glutathione **reductase** by Fenton systems: effect of metal chelators, catecholamines and thiol compounds

AUTHOR(S): Gutierrez-Correa, J.; Stoppani, A. O. M.
CORPORATE SOURCE: Bioenergetics Research Centre, School of Medicine, University of Buenos Aires, Buenos Aires, 1121, Argent.
SOURCE: Free Radical Research (1997), 27(6), 543-555
CODEN: FRARER; ISSN: 1071-5762
PUBLISHER: Harwood Academic Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English

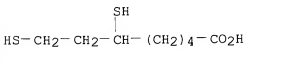
AB Oxygen radical generating systems, namely, Cu(II)/H2O2, Cu(II)/ascorbate, Cu(II)/NAD(P)H, Cu(II)/H2O2/catecholamine and Cu(II)/H2O2/SH-compds. irreversibly inhibited yeast glutathione **reductase** (GR) but Cu(II)/H2O2 enhanced the enzyme diaphorase activity. The time course of GR inactivation by Cu(II)/H2O2 depended on Cu(II) and H2O2 concns. and was relatively slow, as compared with the effect of Cu(II)/ascorbate. The fluorescence of the enzyme Tyr and Trp residues was modified as a result of oxidative damage. Copper chelators, catalase, bovine serum albumin and HO.bul. scavengers prevented GR inactivation by Cu(II)/H2O2 and related systems. Cysteine, N-acetylcysteine, N-(2-mercaptopropionyl)glycine) and penicillamine enhanced the effect of Cu(II)/H2O2 in a concn.- and time-dependent manner. GSH, captopril, **dihydrolipoic acid** and dithiothreitol also enhanced the Cu(II)/H2O2 effect, their actions involving the simultaneous operation of pro-oxidant and antioxidant reactions. GSSG and trypanothione disulfide effectively protected GR against Cu(II)/H2O2 inactivation. Thiol compds. prevented GR inactivation by the radical cation ABTS.bul.+. GR inactivation by the systems assayed correlated with their capability for HO.bul. radical generation. The role of amino acid residues at GR active site as targets for oxygen radicals is discussed.

IT **51-61-6, Dopamine**, biological studies **462-20-4 , Dihydrolipoic acid**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(inactivation of yeast glutathione **reductase** by Fenton systems and effect of metal chelators, catecholamines and thiol compds.)

RN 51-61-6 HCAPLUS
CN 1,2-Benzenediol, 4-(2-aminoethyl)- (9CI) (CA INDEX NAME)



RN 462-20-4 HCAPLUS
CN Octanoic acid, 6,8-dimercapto- (8CI, 9CI) (CA INDEX NAME)



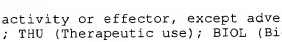
L14 ANSWER 22 OF 29 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:28259 HCAPLUS

DOCUMENT NUMBER: 126:69570
TITLE: .alpha.-**Lipoic acid**: a **metabolic antioxidant** and potential redox modulator of transcription
AUTHOR(S): Packer, Lester; Roy, Sashwati; Sen, Chandan K.
CORPORATE SOURCE: Department of Molecular and Cell Biology, University of California at Berkeley, Berkeley, CA, 94720, USA
SOURCE: Advances in Pharmacology (San Diego) (1997), 38(Antioxidants in Disease Mechanisms and Therapy), 79-101
CODEN: ADPHEL; ISSN: 1054-3589
PUBLISHER: Academic
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with many refs. There has been a great deal of interest in the antioxidant properties of .alpha.-**lipoic acid**, which has long been known as an essential cofactor in oxidative metab. This review discusses the metabolic role as well as the antioxidant properties of .alpha.-**lipoic acid** and its **reduced** form dihydrolipoate. In addn., the effects of this antioxidant in modulating the redox-sensitive transcription factor nuclear factor .kappa.B (NF-.kappa.B) are evaluated. Because NF-.kappa.B is involved in a wide variety of acute inflammatory responses, as well as many other aspects of rapid responses in cells, the authors have chosen this system to explore the action of .alpha.-**lipoic acid** and dihydrolipoate on transcription factors.

IT **462-20-4**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(.alpha.-**lipoic acid** as **metabolic antioxidant** and potential redox modulator of transcription)

RN 462-20-4 HCAPLUS
CN Octanoic acid, 6,8-dimercapto- (8CI, 9CI) (CA INDEX NAME)



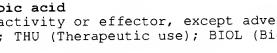
L14 ANSWER 23 OF 29 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1996:745103 HCAPLUS
DOCUMENT NUMBER: 126:18289
TITLE: Neuroprotection by the **metabolic antioxidant** .alpha.-**lipoic acid**
AUTHOR(S): Packer, Lester; Tritschler, Hans J.; Wessel, Klaus
CORPORATE SOURCE: Department Molecular Cell Biology, University California, Berkeley, CA, 94720-3200, USA
SOURCE: Free Radical Biology & Medicine (1996), Volume Date 1997, 22(1/2), 359-378
CODEN: FRBMEH; ISSN: 0891-5849
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Reactive oxygen species are thought to be involved in a no. of types of acute and chronic pathol. conditions in the brain and neural tissue. The **metabolic antioxidant** .alpha.-lipoate (thioctic acid, 1,

2-dithiolane-3-pentanoic acid; 1, 2-dithiolane-3 valeric acid; and 6,8-dithiooctanoic acid) is a low mol. wt. substance that is absorbed from the diet and crosses the blood-brain barrier. .alpha.-Lipoate is taken up and **reduced** in cells and tissues to dihydrolipoate, which is also exported to the extracellular medium; hence, protection is afforded to both intracellular and extracellular environments. Both .alpha.-lipoate and esp. dihydrolipoate have been shown to be potent antioxidants, to regenerate through redox cycling other antioxidants like vitamin C and vitamin E, and to raise intracellular glutathione levels. Thus, it would seem an ideal substance in the treatment of oxidative brain and neural disorders involving free radical processes. Examn. of current research reveals protective effects of these compds. in cerebral ischemia-reperfusion, excitotoxic amino acid brain injury, mitochondrial dysfunction, diabetes and diabetic neuropathy, inborn errors of metab., and other causes of acute or chronic damage to brain or neural tissue. Very few neuropharmacol. intervention strategies are currently available for the treatment of stroke and numerous other brain disorders involving free radical injury. We propose that the various **metabolic antioxidant** properties of .alpha.-lipoate relate to its possible therapeutic roles in a variety of brain and neuronal tissue pathologies: thiols are central to antioxidant defense in brain and other tissues. The most important thiol antioxidant, glutathione, cannot be directly administered, whereas .alpha.-**lipoic acid** can. In vitro, animal, and preliminary human studies indicate that .alpha.-lipoate may be effective in numerous neurodegenerative disorders.

IT **462-20-4, Dihydrolipoic acid**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(neuroprotection by the **metabolic antioxidant** .alpha.-**lipoic acid**)

RN 462-20-4 HCAPLUS
CN Octanoic acid, 6,8-dimercapto- (8CI, 9CI) (CA INDEX NAME)

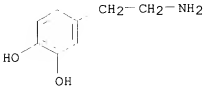


L14 ANSWER 24 OF 29 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1996:457381 HCAPLUS
DOCUMENT NUMBER: 125:133465
TITLE: Catecholamines enhance dihydrolipoamide dehydrogenase inactivation by the copper Fenton system. Enzyme protection by copper chelators
AUTHOR(S): Correa, Gutierrez J.; Stoppani, A. O. M.
CORPORATE SOURCE: Bioenergetics Research Center, University of Buenos Aires, Buenos Aires, Argent.
SOURCE: Free Radical Research (1996), 24(4), 311-322
CODEN: FRARER; ISSN: 1071-5762
PUBLISHER: Harwood
DOCUMENT TYPE: Journal
LANGUAGE: English

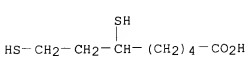
AB Catecholamines (CA: epinephrine, norepinephrine, **dopamine**, L-DOPA, 6-**hydroxydopamine**) and o-diphenols (DOPAC and catechol) enhanced dihydrolipoamide dehydrogenase (LADH) inactivation by Cu (II)/H2O2 (Cu-Fenton system). The inhibition of LADH activity correlated with Cu(II)/H2O2 and CA concns. Similar inhibitions were obtained with

the assayed CAs and o-diphenols. CAs enhanced HO.ovrhdot. radical prodn. by Cu(II)/H2O2, as demonstrated by benzoate hydroxylation and deoxyribose oxidn.; LADH counteracted the pro-oxidant effect of CAs by scavenging hydroxyl radicals. Captopril, dihydrolipoamide, **dihydrolipoic acid**, DL-dithiothreitol, GSSG, trypanothione and histidine effectively preserved LADH from oxidative damage, whereas N-acetylcysteine, N-(2-mercaptopropionyl)glycine) and lipoamide were **less** effective protectors. Catalase (though neither bovine serum albumin nor superoxide dismutase) protected LADH against the Cu(II)/H2O2/CAs systems. Denatured catalase protected **less** than the native enzyme, its action possibly depending on Cu-binding. LADH increased and Captopril inhibited epinephrine oxidn. by Cu(II)/H2O2 and Cu(II). The summarized evidence supports the following steps for LADH inactivation: (1) **redn.** of LADH linked-Cu(II) to Cu(I) by CAs; (2) prodn. of HO.ovrhdot. from H2O2 by LADH-linked Cu(I) (Haber-Weiss reaction) and (3) oxidn. of amino acid residues at the enzyme active site by site-specifically generated HO.ovrhdot. radicals. Hydrogen peroxide formation from CAs autoxidn. may contribute to LADH inactivation.

IT **51-61-6, Dopamine,** biological studies
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(copper chelator protection against catecholamine enhancement of dihydrolipoamide dehydrogenase inactivation by the copper Fenton system)
RN 51-61-6 HCAPLUS
CN 1,2-Benzenediol, 4-(2-aminoethyl)- (9CI) (CA INDEX NAME)

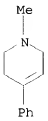


IT **462-20-4, Dihydrolipoic acid**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(copper chelator protection against catecholamine enhancement of dihydrolipoamide dehydrogenase inactivation by the copper Fenton system)
RN 462-20-4 HCAPLUS
CN Octanoic acid, 6,8-dimercapto- (8CI, 9CI) (CA INDEX NAME)



L14 ANSWER 25 OF 29 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1995:433039 HCAPLUS
DOCUMENT NUMBER: 122:204971
TITLE: Influence of N-methyl-4-phenyl-1,2,3,6,-tetrahydropyridine, **lipoic acid** and L-deprenyl on the interplay between cellular redox systems
AUTHOR(S): Goetz, M.E.; Dirr, A.; Gsell, W.; Burger, R.; Janetzky, B.; Freyberger, A.; Reichmann, H.; Rausch,

W.-D.; Riederer, P.
CORPORATE SOURCE: Department of Psychiatry, University of Wuerzburg, Wuerzburg, Germany
SOURCE: Journal of Neural Transmission, Supplement (1994), 43(Neuroprotection in Neurodegeneration), 145-62
CODEN: JNTSD4; ISSN: 0303-6995
DOCUMENT TYPE: Journal
LANGUAGE: English
AB For several years there is controversy concerning the toxic potency of reaction products catalyzed by monoamine oxidase in neurodegenerative processes. There is uncertainty whether products of catecholamine oxidn. are pathogenetically relevant factors for neuronal cell death in Parkinson's disease. To date products responsible for impairment of biochem. functions essential for cell viability are not yet identified, and the primary site of damage within the cell is unknown. Ammonia, aldehydes and hydrogen peroxide are formed via monoamine oxidase catalyzed oxidns. of primary amines. But which of them, if any, is damaging to the cell. We discuss some aspects of the oxidative stress theory of cell degeneration in relation to toxicity of N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (**MPTP**) and to monoamine oxidn. Furthermore, we consider possible functional relationships of mitochondrial electron transfer reactions, toxicity of **MPTP** and MAO activity.
IT **28289-54-5**, N-Methyl-4-phenyl-1,2,3,6,-tetrahydropyridine
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(influence of N-methyl-4-phenyl-1,2,3,6,-tetrahydropyridine, **lipoic acid** and L-deprenyl on interplay between cellular redox systems)
RN 28289-54-5 HCAPLUS
CN Pyridine, 1,2,3,6-tetrahydro-1-methyl-4-phenyl- (6CI, 7CI, 8CI, 9CI) (CA INDEX NAME)



L14 ANSWER 26 OF 29 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1994:499091 HCAPLUS
DOCUMENT NUMBER: 121:99091
TITLE: **Lipoic acid** favors thiosulfinate formation after hypochlorous acid scavenging: a study with **lipoic acid** derivatives
AUTHOR(S): Biewenga, Gerreke Ph.; de Jong, Jan; Bast, Aalt
CORPORATE SOURCE: Leiden/Amsterdam Center for Drug Research, Vrije Universiteit, Amsterdam, 1081 HV, Neth.
SOURCE: Archives of Biochemistry and Biophysics (1994), 312(1), 114-20
CODEN: ABBIA4; ISSN: 0003-9861
DOCUMENT TYPE: Journal
LANGUAGE: English
AB **Lipoic acid**, the oxidized form of 6,8-

dimercaptooctanoic acid has a strained cyclic disulfide in a 1,2-dithiolane ring. Recently its antioxidant activity gained attention. Hypochlorous acid (HOCl) is an oxidant produced by neutrophils. A prominent effect of HOCl is the inactivation of .alpha.-1-antiproteinase to inhibit elastase is lost. The resulting higher activity of elastase is held responsible for tissue damage in lung emphysema. The authors studied the HOCl scavenging capability of three metabolites of **lipoic acid**: tetranor-, bisnor-, and .beta.-**lipoic acid**. To obtain some insight on the mol. basis of HOCl scavenging 1,2-dithiane-4,5-diol, cystine, **lipoic acid** Me ester, and lipoamide were also included in the study. The extent of .alpha.-1-antiproteinase inactivation by HOCl in the presence of scavenger was taken as a parameter to quantify the scavenging activity. It was found that **lipoic acid**, tetranor- and **bisnorlipoic acid**, **lipoic acid** Me ester, and lipoamide all showed the same activity toward HOCl. .beta.-**Lipoic acid**, 1,2-dithiane-4,5-diol and cystine were **less** active. The products of **lipoic acid** after reaction with HOCl were studied using GC/MS. Indications for thiol-sulfinate formation were found by comparing these products with the GC/MS profile of .beta.-**lipoic acid**. Thiolsulfinate formation may also be suggested in the reaction of tetranor- and **bisnorlipoic acid** and **lipoic acid** Me ester with HOCl. The present results show an antioxidant activity of the metabolites tetranor- and **bisnorlipoic acid**. The 1,2-dithiolane ring may enhance the reactivity toward HOCl compared to **less** strained disulfides, resulting in the formation a thiolsulfinate.

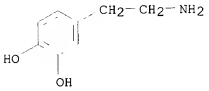
L14 ANSWER 27 OF 29 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER:	1994:208505 HCAPLUS
DOCUMENT NUMBER:	120:208505
TITLE:	Effect of **lipoic acid** on redox state of coenzyme Q in mice treated with 1-methyl-4-phenyl-1,2,3,6-**tetrahydropyridine** and diethyldithiocarbamate
AUTHOR(S):	Goetz, Mario E.; Dirr, Albrecht; Burger, Rainer; Janetzky, Bernd; Weinmueller, Markus; Chan, Wing W.; Chen, Shih C.; Reichmann, Heinz; Rausch, Wold Dieter; Riederer, Peter
CORPORATE SOURCE:	Dep. Psychiatry, Univ. Wuerzburg, Wuerzburg, Germany
SOURCE:	European Journal of Pharmacology, Molecular Pharmacology Section (1994), 266(3), 291-300 CODEN: EJPPET; ISSN: 0922-4106
DOCUMENT TYPE:	Journal
LANGUAGE:	English

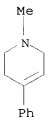
AB The authors investigated the effects of a combined treatment of male C57Bl/6 mice with diethyldithiocarbamate and 1-methyl-4-phenyl-1,2,3,6-**tetrahydropyridine** (**MPTP**) in the absence or presence of different forms of **lipoic acid** (Thioctacid T; commonly used for treatment of diabetic polyneuropathies) on levels and redox states of .alpha.-tocopherol and coenzyme Q in vivo and on activities of various enzymes of energy metab. ex vivo. Treatment of mice with diethyldithiocarbamate plus **MPTP** resulted in a decrease in **dopamine** (67%) and its major metabolites dihydroxyphenylacetic acid (38%) and homovanillic acid (37%) in striatum. .alpha.-Tocopherol levels were unaltered in striatum; however, the **reduced** forms of coenzyme Q were decreased in frontal cortex and hippocampus following diethyldithiocarbamate plus **MPTP**. In frontal cortex activity of NADH dehydrogenase was significantly inhibited by diethyldicarbamate plus

MPTP ex vivo, suggesting that the neurotoxic metabolite of **MPTP**, 1-methyl-4-phenylpyridinium ion, is acting in brain regions other than striatum as well. **Lipoic acid**, administered 6 times, each at 90 min prior to **MPTP**, could not restore **dopamine** in striatum but in contrast maintained a normal ratio of the **reduced** form to the oxidized form of coenzyme Q, suggesting an interaction of **lipoic acid** with energy metab. which seems, however, not only to be due to an activation of pyruvate dehydrogenase.

IT **51-61-6, Dopamine**, biological studies
RL: BIOL (Biological study)
(in brain redox state induced by **MPTP** and diethyldithiocarbamate, **lipoic acid** effect on)
RN 51-61-6 HCAPLUS
CN 1,2-Benzenediol, 4-(2-aminoethyl)- (9CI) (CA INDEX NAME)



IT **28289-54-5, MPTP**
RL: BIOL (Biological study)
(**lipoic acid** effect on coenzyme Q in brain redox state induced by diethyldithiocarbamate and)
RN 28289-54-5 HCAPLUS
CN Pyridine, 1,2,3,6-tetrahydro-1-methyl-4-phenyl- (6CI, 7CI, 8CI, 9CI) (CA INDEX NAME)



L14 ANSWER 28 OF 29 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER:	1987:454715 HCAPLUS
DOCUMENT NUMBER:	107:54715
TITLE:	Quantitative studies of **hydroperoxide reduction** by prostaglandin H synthase. **Reducing** substrate specificity and the relationship of peroxidase to cyclooxygenase activities
AUTHOR(S):	Markey, Christine M.; Alward, Abdo; Weller, Paul E.; Marnett, Lawrence J.
CORPORATE SOURCE:	Dep. Chem., Wayne State Univ., Detroit, MI, 48202, USA
SOURCE:	Journal of Biological Chemistry (1987), 262(13), 6266-79 CODEN: JBCHA3; ISSN: 0021-9258
DOCUMENT TYPE:	Journal

LANGUAGE: English
AB The peroxidase activity of prostaglandin H (PGH) synthase catalyzes **redn.** of 5-phenyl-4-pentenyl **hydroperoxide** to 5-phenyl-4-pentenyl alc. with a turnover no. of .apprx.8000 mol of 5-phenyl-4-pentenyl **hydroperoxide**/mol of enzyme/min. The kinetics and products of reaction establish PGH synthase as a classical heme peroxidase with catalytic efficiency similar to horseradish peroxidase. This suggests that the protein of PGH synthase evolved to facilitate peroxide heterolysis by the heme prosthetic group. Comparison of an extensive series of phenols, arom. amines, .beta.-carbonyls, naturally occurring compds., and nonsteroidal anti-inflammatory drugs indicates that considerable differences exist in their ability to act as **reducing** substrates. No correlation is obsd. between the ability of compds. to support peroxidatic **hydroperoxide redn.** and to inhibit cyclooxygenase. In addn., the resolved enantiomers of MK-410 and etodolac exhibit dramatic enantiospecific differences in their ability to inhibit cyclooxygenase but are equally potent as peroxidase-**reducing** substrates. This suggests that there are significant differences in the orientation of compds. at cyclooxygenase inhibitory sites and the peroxidase oxidn. site(s). Comparison of 5-phenyl-4-pentenyl **hydroperoxide redn.** by PGH synthase and horseradish peroxidase reveals considerable differences in **reducing** substrate specificity. Both the cyclooxygenase and peroxidase activities of PGH synthase inactivate in the presence of low micromolar amts. of **hydroperoxides** and arachidonic acid. PGH synthase was most sensitive to arachidonic acid, which exhibited a concn. for 50% inhibition (I50) of 0.6 .mu.M in the absence of all protective agents. Inactivation by **hydroperoxides** requires peroxidase turnover and can be prevented by **reducing** substrates. The I50 values for inactivation by 15-**hydroperoxy**-5,8,11,13-eicosatetraenoic acid are 4.0 and 92 .mu.M, resp., in the absence and presence of 500 .mu.M phenol, a moderately good **reducing** substrate. The ability of compds. to protect against **hydroperoxide**-induced inactivation correlates directly with their ability to act as **reducing** substrates. Hydroquinone, an excellent **reducing** substrate, protected against **hydroperoxide**-induced inactivation when present in <3-fold molar excess over **hydroperoxide**. The presence of a highly efficient **hydroperoxide-reducing** activity appears absolutely essential for protection of the cyclooxygenase capacity of PGH synthase. The peroxidase activity is, therefore, a twin-edged sword, responsible for and protective against **hydroperoxide**-dependent inactivation of PGH synthase. As such, it may constitute an important target for pharmacol. modulation of eicosanoid biosynthesis.

L14 ANSWER 29 OF 29 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1977:85309 HCAPLUS
DOCUMENT NUMBER: 86:85309
TITLE: Inhibition of prostaglandin endoperoxide synthetase by thiol analogs of prostaglandin
AUTHOR(S): Ohki, Shiro; Ogino, Nobuchika; Yamamoto, Shozo; Hayaishi, Osamu; Yamamoto, Hisashi; Miyake, Hazimu; Hayashi, Masaki
CORPORATE SOURCE: Fac. Med., Kyoto Univ., Kyoto, Japan
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (1977), 74(1), 144-8
CODEN: PNASA6; ISSN: 0027-8424
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A variety of SH compds. inhibited the enzymic bis-oxygenation of

8,11,14-eicosatrienoic acid to prostaglandin G1 (I), as examd. with a purified prepn. of prostaglandin endoperoxide synthetase (prostaglandin synthase; EC 1.14.99.1) of bovine vesicular gland. The **hydroperoxide** cleavage of I producing prostaglandin H1 was not affected by these SH compds. Several prostaglandin analogs with an SH group (9,11-dihydroxy-15-mercaptoprosta-5,13-dienoic acid (II), R and S forms, 1-mercapto-9,11,15-trihydroxyprosta-5,13-diene, and 1-mercapto-9-oxo-11,15-dihydroxyprosta-5,13-diene) were most potent inhibitors, showing almost complete inhibition at concns. of .apprx.1 .mu.M. Other SH compds., such as 2,3-dimercaptopropanol (III), dithiothreitol, and **dihydrolipoic acid**, were also inhibitory but were much **less** effective. The inhibition, by S-II and III, was noncompetitive.

Other Databases -for Compd A OR B combined with Test Terms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=> d que stat l22
L1             1 SEA FILE=REGISTRY ABB=ON  3737-39-1/RN
L3             1 SEA FILE=REGISTRY ABB=ON  7516-48-5/RN
L5            23 SEA FILE=HCAPLUS ABB=ON  (L1 OR PHENYL?(W)2(W)?THIOPHENECARBOXI
                 MID? OR ?PHENYL2THIOPHENECARBOXIMID?)
L6          3038 SEA FILE=HCAPLUS ABB=ON  (L3 OR ?LIPOIC?(W)?ACID? OR ?OCTANOIC?
                 (W)?ACID?(3A)(?DIMERCAPTO? OR DI(W)?MERCAPTO?))
L8          3060 SEA FILE=HCAPLUS ABB=ON  L5 OR L6
L9             1 SEA FILE=REGISTRY ABB=ON  MPTP/CN
L10            2 SEA FILE=HCAPLUS ABB=ON  L8 AND (L9 OR ?MPTP?)
L11            1 SEA FILE=REGISTRY ABB=ON  DOPAMINE/CN
L12           53 SEA FILE=HCAPLUS ABB=ON  L8 AND (L11 OR ?DOPAMIN? OR ?METABOL?(
                 W)?ANTIOXID? OR ?SYNTHAS?(W)?INHIBIT?)
L13           28 SEA FILE=HCAPLUS ABB=ON  L12 AND (?FALL? OR ?REDUC? OR
                 ?MINIMIZ? OR ?LESS? OR ?DROP?)
L14           29 SEA FILE=HCAPLUS ABB=ON  L10 OR L13
L21           55 SEA L14
L22           40 DUP REMOV L21 (15 DUPLICATES REMOVED)

=> d ibib abs l22 1-40

L22  ANSWER 1 OF 40  EMBASE  COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER:    2003073850  EMBASE
TITLE:               Oxidative stress in neurodegenerative diseases: Therapeutic
                     implications for superoxide dismutase mimetics.
AUTHOR:              Pong K.
CORPORATE SOURCE:    Dr. K. Pong, Department of Neuroscience, Wyeth Research,
                     Princeton, NJ 08543, United States. pongk@wyeth.com
SOURCE:              Expert Opinion on Biological Therapy, (2003) 3/1 (127-139).
                     Refs: 154
                     ISSN: 1471-2598  CODEN: EOBTA2
COUNTRY:             United Kingdom
DOCUMENT TYPE:       Journal; General Review
FILE SEGMENT:        005     General Pathology and Pathological Anatomy
                     008     Neurology and Neurosurgery
                     029     Clinical Biochemistry
                     037     Drug Literature Index
                     039     Pharmacy
LANGUAGE:            English
SUMMARY LANGUAGE:    English
AB   Evidence of oxidative stress is apparent in both acute and chronic
     neurodegenerative diseases, such as stroke, Parkinson's disease (PD) and
     amyotrophic lateral sclerosis (ALS). Increased generation of reactive
     oxygen species simply overwhelm endogenous antioxidant defences, leading
     to subsequent oxidative damage and cell death. Tissue culture and animal
     models have been developed to mimic some of the biochemical changes and
     neuropathology found in these diseases. In doing so, it has been
     experimentally demonstrated that oxidative stress plays a critical role in
     neuronal cell death. Antioxidant enzymes, such as superoxide dismutase
     (SOD), catalase and glutathione peroxidase (GPx) have demonstrated
     therapeutic efficacy in models of neurodegeneration. However, delivery and
     stability issues have reduced the enthusiasm to clinically
     develop these proteins. Most recently, SOD mimetics, small molecules which
     mimic the activity of endogenous superoxide dismutase, have come to the
     forefront of antioxidant therapeutics. This review will examine the
     experimental evidence supporting the use of scavengers of superoxide
     anions in treating some neurodegenerative diseases, such as stroke, PD and
     ALS, but also the pitfalls that have met antioxidant molecules
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in clinical trials.

L22 ANSWER 2 OF 40 WPIDS (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 2003-167299 [16] WPIDS
CROSS REFERENCE: 2002-096565 [13]
DOC. NO. CPI: C2003-043434
TITLE: Treatment of skin, hair or nails to render them more uniform and smoother involves use of a composition containing an alkanolamine compound.
DERWENT CLASS: B04 D21 E16
INVENTOR(S): PERRICONE, N V
PATENT ASSIGNEE(S): (PERR-I) PERRICONE N V
COUNTRY COUNT: 100
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2002098515	A2	20021212	(200316)*	EN	18

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW

US 6500857	B1	20021231	(200316)		
US 2003017177	A1	20030123	(200316)		
US 2003021855	A1	20030130	(200316)		

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
WO 2002098515	A2		WO 2002-US18026	20020606
US 6500857	B1		US 2001-931616	20010816
US 2003017177	A1		US 2001-900680	20010706
US 2003021855	A1	CIP of	US 2001-900680	20010706
			US 2002-85864	20020227

PRIORITY APPLN. INFO: US 2002-85864 20020227; US 2001-875317 20010606; US 2001-900680 20010706; US 2001-931616 20010816

AN 2003-167299 [16] WPIDS
CR 2002-096565 [13]
AB WO 200298515 A UPAB: 20030307
NOVELTY - Treatment of skin, hair or nails to render them more uniform and smoother involves application of a composition containing an alkanolamine compound.

DETAILED DESCRIPTION - Treatment of skin, hair or nails to render them more uniform and smoother involves application of a composition (C1) containing an alkanolamine compound of formula (I).

X, Y, Z = H, 1-3C alkyl or 2-4C alkanol.

Provided that at least one of X, Y or Z is 2-4C alkanol containing at least one OH group and optionally at least one carboxyl group.

ACTIVITY - Antiseborrheic; Dermatological.

A phospholipid-based lotion containing (wt.%) dimethylaminoethanol (5), tyrosine (5) and **lipoic acid** (1-3) was applied to facial skin of test subjects. Pore size was visibly **reduced** in all subject within an hour. In an open, unblinded study involving twice

daily application of the composition over 2-3 months to subjects presenting with uneven skin having enlarged pores and a few blemishes resulted in a very pronounced smoother, more porcelain-like complexion of treated subjects when compared to the uneven, ruddy complexion of control subjects.

MECHANISM OF ACTION - None given.

USE - The composition is used in the treatment of skin, hair or nails to render them more uniform and smooth, for the treatment and prevention of acne, and the inhibition of cutaneous scar tissue (all claimed).

ADVANTAGE - The method visibly **reduces** the pore size, evens skin texture and gives a more attractive and youthful appearance. Application to the hair, fingernails or toenails, increases elasticity, smoothness, surface uniformity, enhances shine, and provides emolliency to keratin. Treated hair becomes softer, shinier and more manageable, and nails become **less** brittle and more lustrous.

Dwg.0/0

L22 ANSWER 3 OF 40 WPIDS (C) 2003 THOMSON DERWENT

ACCESSION NUMBER:	2002-590578 [63] WPIDS
DOC. NO. NON-CPI:	N2002-468664
DOC. NO. CPI:	C2002-167041
TITLE:	Dispensing a therapeutic agent in situ to a localized region e.g. a tumor useful for gene therapy comprises administering a polymer composition, a cross-linking composition and the therapeutic agent to the region.
DERWENT CLASS:	A96 B04 B05 D16 P31
INVENTOR(S):	AZHDARINIA, A; KIM, E E; LEE, T L; YANG, D J; YU, D
PATENT ASSIGNEE(S):	(TEXA) UNIV TEXAS SYSTEM
COUNTRY COUNT:	98

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2002049501	A2	20020627	(200263)*	EN	116

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW

W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZM ZW

AU 2002031041 A 20020701 (200264)

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2002049501	A2	WO 2001-US49087	20011218
AU 2002031041	A	AU 2002-31041	20011218

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2002031041	A Based on	WO 200249501

PRIORITY APPLN. INFO: US 2000-256514P 20001218

AN 2002-590578 [63] WPIDS

AB WO 200249501 A UPAB: 20021031

NOVELTY - Dispensing (M1) a therapeutic agent in situ to a localized region in an individual comprising administering a biocompatible polymer

composition (a), a cross-linking composition (b) and the therapeutic agent to the region to allow formation of a cross-linked polymer in situ at the region, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:

(1) treating a tumor in situ, occluding an artery associated with a tumor in an individual or providing a slow-release hydrogel composition in situ to a tumor involving administering to the tumor (a), (b) and the therapeutic agent; and

(2) a kit for treating a tumor in situ and for occluding an artery associated with a tumor in an individual comprising, a first container with (a) and a second container with (b) in a container.

ACTIVITY - Cytostatic; Antitumor.

Rats with mammary tumor were used in the study. Cisplatin was suspended in sodium alginate to prepare SA-CDDP (5.4 mg cisplatin/ml). The SA-CDDP (0.1 ml, cisplatin dose was 3 mg/kg body weight) was injected directly into the tumors. Calcium chloride (8% in water) was then injected into the same place to form cisplatin-loaded alginate beads in the tumors. The tumor size was measured to determine the anticancer effect and blood chemical assay (blood urea nitrogen (BUN) and serum creatinine) were performed to detect renal toxicity. After injection, tumor volume decreased as a function of time. No tumor relapse had occurred in the rats 5 months after treatment. BUN and serum creatinine levels after intratumoral injection of SA-CDDP was in the normal range. On day 40, BUN in five experimental rats and five healthy rats (control) were 18.30 plus or minus 1.51 mg/dl and 17.88 plus or minus 2.24 mg/dl respectively. Serum creatinine levels were the same as in both experimental and control rats (0.6 mg/dl). In rats treated with CDDP intratumorally, a clear nephrotoxicity was observed as evidenced by increased BUN and creatinine levels.

MECHANISM OF ACTION - None given.

USE - (M1) is used for dispensing a therapeutic agent in situ to a localized region in an individual, for treating a tumor in situ, for occluding an artery associated with a tumor and for providing a slow-release hydrogel composition in situ to a tumor (claimed), gene therapy, brachytherapy, transcatheter arterial chemoembolization and/or intralesional injection.

ADVANTAGE - (M1) administers in situ an anticancer drug with high loading yields for a drug carrier, absence of leakage into surrounding tissues, lower cost, ease of process and better treatment response. (M1) allows correct dosing, is relatively easy to perform, is cost-effective and generates little waste of expensive chemotherapeutics. (M1) is also useful for tumors where removal by surgery is not a viable option (claimed).

Dwg.0/9

L22 ANSWER 4 OF 40 WPIDS (C) 2003 THOMSON DERWENT

ACCESSION NUMBER:	2002-415383 [44] WPIDS
DOC. NO. NON-CPI:	N2002-326759
DOC. NO. CPI:	C2002-117233
TITLE:	Composition useful in the treatment of obesity comprises at least one micronutrient and target absorbent compound.
DERWENT CLASS:	B04 D13 J04 S03
INVENTOR(S):	BUCHANAN-BAILLIE-HAMILTON, P F; PECK, J C
PATENT ASSIGNEE(S):	(BUCH-I) BUCHANAN-BAILLIE-HAMILTON P F
COUNTRY COUNT:	96

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2002012882	A2	20020214	(200244)*	EN	86

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ
NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK
DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR
KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU
SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2001076537 A 20020218 (200244)
GB 2370504 A 20020703 (200251)

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2002012882	A2	WO 2001-GB3554	20010807
AU 2001076537	A	AU 2001-76537	20010807
GB 2370504	A	GB 2001-17052	20010712

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 2001076537	A	Based on	WO 200212882

PRIORITY APPLN. INFO: GB 2001-17052 20010712; GB 2000-19327 20000808

AN 2002-415383 [44] WPIDS

AB WO 200212882 A UPAB: 20020711
NOVELTY - A composition comprises at least one active compound e.g. micronutrient or target compound absorbent.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following: 1) a method for comparing the relative inhibitory effects of several of target compounds (A1)/items on the ability of a test subject (A2)/(A2) exposed to the items to control their weight involving performing the method for each (A1)/item, and comparing the inhibitory effects of each (A1)/item; 2) a method for labeling and/or certifying an item according to its inhibitory effect on the ability of (A2) exposed to the item to control their weight involving performing the method for the item, and labeling and/or certifying the item based on a pre-determined scale according to their inhibitory effect; 3) a method of diagnosis and/or prognosis of a weight-control-related disorder or disease in (A2) involving performing a method and correlating the results obtained from the method with the disease state of the subject; 4) determining a test subject's progress in altering the extent to which their ability to control their weight has been inhibited involving performing the method at intervals, and comparing the results obtained from the method to establish the progress made; 5) production of a tailored advice plan for (A2) involving performing a method and providing a plan in accordance with the results obtained from the method. The plan provides a system for improving or maintaining the ability of (A2) to control their weight; 6) determining the extent of the inhibitory effect of (A1) on the ability of (A2) into whom (A1) is introduced to control their weight involving (i) determining the degree or severity by which (A1) affects each of several weight controlling systems (HICS) present in (A2); (ii) determining the persistence of (A1) in (A2); (iii) calculating the inhibitory effect as a function of values of (i) and (ii); 7) Use of the composition in the preparation of a medicament for the treatment of obesity; 8) production of a database of the inhibitory effects of several (A1)/items on the ability of (A2)/(A2) exposed to the items to control their weight involving performing the method for each (A1)/items, and combining the results into a database; 9) computer system for use in the performance of a method or

displaying the output of the method, or displaying or accessing the database, comprising (a) a standard electronic computer circuit containing at least a random access memory, a read only memory, a processor; (b) a keyboard comprising several standard keyboard buttons; and (c) a display; 11) production of a labeled and/or certified item, involving providing the item to be labeled and/or certified, and performing the method on the item; 12) a database produced by the method; 13) a data carrier comprising the database; 14) determining the inhibitory effect of an item on the ability of (A2) exposed to the item to control their weight involving: a1) optionally determining the amount of each of several (A1) in the item having an inhibitory effect on the ability of (A2) to control their weight; and 15) a system for improving or maintaining the ability of (A2) to control their weight including (a) a commodity provider, which provides commodities for (A2), (b) a certifier which certifies each commodity according to its inhibitory effect on the ability of (A2) exposed to the item to control their weight such that the subject can select each commodity to its certification. The certifier optionally uses an analyzer for determining the presence of (A1) in each commodity and a database of the inhibitory effect of (A1) present in the commodity on the ability of (A2) to control their weight.

ACTIVITY - Anorectic; Cardiant; Antiasthmatic; Antiallergic; Cytostatic; Dermatological; Immunosuppressive.

MECHANISM OF ACTION - Inhibitor.

USE - For cosmetic improvement of the subject, which does not suffer from obesity; for treatment of the subject suffering from obesity; for use in a method for treatment of obesity; for controlling the weight of the subject; in the preparation of the medicament for the treatment of obesity (all claimed); for the control and treatment of various conditions associated with obesity e.g. immune dysfunction, autoimmunity, cardiovascular disorder, pulmonary disorder (e.g. asthma), allergies, cancer, mood changes, neurological illness, changes in libido, hormonal disorders, reproductive dysfunction, congenital abnormalities, metabolic disorder (e.g. glucose dysregulation), muscular skeletal disorder, renal and genitourinary disorder and skin disorder.

ADVANTAGE - The composition achieves significantly more effective and long lasting weight **reduction** without the use of drugs which interferes with the body's natural metabolism, by means of effectively restoring the body's own natural slimming system in a substantially natural manner.

Dwg.0/9

L22 ANSWER 5 OF 40 WPIDS (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 2002-731368 [79] WPIDS
CROSS REFERENCE: 2002-290892 [33]
DOC. NO. CPI: C2002-207151
TITLE: Composition used for treating arthritis comprises nitric oxide production inhibitor and aminosugar.
DERWENT CLASS: B05
INVENTOR(S): PETRUS, E J
PATENT ASSIGNEE(S): (PETR-I) PETRUS E J
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
US 2002119952	A1	20020829	(200279)*		7

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE

US 2002119952 A1	CIP of	US 1998-149241	19980908
	CIP of	US 1999-350380	19990708
		US 2002-68249	20020205

FILING DETAILS:

PATENT NO	KIND	PATENT NO
US 2002119952 A1	CIP of	US 6346519

PRIORITY APPLN. INFO: US 2002-68249 20020205; US 1998-149241 19980908; US 1999-350380 19990708

AN 2002-731368 [79] WPIDS
CR 2002-290892 [33]
AB US2002119952 A UPAB: 20021209
NOVELTY - Composition comprises a nitric oxide production inhibitor and an aminosugar.

ACTIVITY - Antiarthritic; Antirheumatic; Osteopathic; Analgesic.

A 58 year old male with osteoarthritis of both knees was started on a commercial composition (control) of glucosamine hydrochloride (500 mg) and chondroitin sulfate (400 mg) taken 3 times a day for 6 months. The relief from pain and limitation of motion was inconsistent. The male was given a composition (test) comprising zinc acetate (20 mg) and glucosamine sulfate (500 mg) coated with polyvinyl pyrrolidone (7 mg) 3 times a day. By day 21 the knee pain subsided and range of motion was unrestricted. A maintenance dose of glucosamine sulfate (500 mg) and zinc acetate (10 mg) was continued for six months and the pain relief and range of motion of the knees were maintained.

MECHANISM OF ACTION - Nitric oxide production inhibitor.

USE - Used for treating arthritis, particularly rheumatoid arthritis and osteoarthritis, repairing of articular joint surfaces and relief of symptoms associated with arthritis.

ADVANTAGE - The composition **reduces** the level of nitric oxide, free radicals responsible for the degradation of articular cartilage.

Dwg.0/0

L22 ANSWER 6 OF 40 WPIDS (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 2002-290892 [33] WPIDS
CROSS REFERENCE: 2002-731368 [79]
DOC. NO. CPI: C2002-085253
TITLE: Composition useful for treatment of arthritis comprises nitric oxide **synthase inhibitor** and an amino sugar.
DERWENT CLASS: B05
INVENTOR(S): PETRUS, E J
PATENT ASSIGNEE(S): (ADME-N) ADVANCED MEDICAL INSTR
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
US 6346519	B1	20020212	(200233)*		6

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
US 6346519	B1	CIP of	US 1998-149241	19980909

PRIORITY APPLN. INFO: US 1999-350380 19990708; US 1998-149241 19980909
AN 2002-290892 [33] WPIDS
CR 2002-731368 [79]
AB US 6346519 B UPAB: 20021212
NOVELTY - A composition comprises nitric oxide **synthase inhibitor** (I) and an aminosugar (II).
ACTIVITY - Antiarthritic; Osteopathic.
No specific biological data given.
MECHANISM OF ACTION - Nitric oxide **synthase inhibitor**.
USE - For treating arthritis (claimed) and osteoarthritis. Also for repairing of articular joint surfaces and the relief of symptoms associated with arthritis.
ADVANTAGE - (I) **reduces** the level of nitric oxide, the free radical responsible for the degradation of articular cartilage. (II) are building blocks of articular cartilage and have anti-inflammatory action.
Dwg.0/0

L22 ANSWER 7 OF 40 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2002:587405 BIOSIS
DOCUMENT NUMBER: PREV200200587405
TITLE: Glutathione, iron and Parkinson's disease.
AUTHOR(S): Bharath, Srinivas; Hsu, Michael; Kaur, Deepinder; Rajagopalan, Subramanian; Andersen, Julie K. (1)
CORPORATE SOURCE: (1) Buck Institute For Age Research, 8001 Redwood Boulevard, Novato, CA, 94945: jandersen@buckinstitute.org USA
SOURCE: Biochemical Pharmacology, (September, 2002) Vol. 64, No. 5-6, pp. 1037-1048. http://www.elsevier.com/locate/biochemp harm. print.
ISSN: 0006-2952.
DOCUMENT TYPE: General Review
LANGUAGE: English
AB Parkinson's disease (PD) is a progressive neurodegenerative disease involving neurodegeneration of **dopaminergic** neurons of the substantia nigra (SN), a part of the midbrain. Oxidative stress has been implicated to play a major role in the neuronal cell death associated with PD. Importantly, there is a drastic depletion in cytoplasmic levels of the thiol tripeptide glutathione within the SN of PD patients. Glutathione (GSH) exhibits several functions in the brain chiefly acting as an antioxidant and a redox regulator. GSH depletion has been shown to affect mitochondrial function probably via selective inhibition of mitochondrial complex I activity. An important biochemical feature of neurodegeneration during PD is the presence of abnormal protein aggregates present as intracytoplasmic inclusions called Lewy bodies. Oxidative damage via GSH depletion might also accelerate the build-up of defective proteins leading to cell death of SN **dopaminergic** neurons by impairing the ubiquitin-proteasome pathway of protein degradation. Replenishment of normal glutathione levels within the brain may hold an important key to therapeutics for PD. Several reports have suggested that iron accumulation in the SN patients might also contribute to oxidative stress during PD.

L22 ANSWER 8 OF 40 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 1
ACCESSION NUMBER: 2003:23904 BIOSIS
DOCUMENT NUMBER: PREV200300023904

TITLE: Effect of DL-alpha-**lipoic acid** on the status of lipid peroxidation and protein oxidation in various brain regions of aged rats.
AUTHOR(S): Arivazhagan, Palaniappan; Thilakavathy, Thangaswamy; Ramanathan, Kadirvel; Kumaran, Sundaram; Panneerselvam, Chinnakkannu (1)
CORPORATE SOURCE: (1) Department of Medical Biochemistry, Dr. AL Mudaliar PG Institute of Basic Medical Sciences, University of Madras, Taramani, Chennai, 600 113, India: panneerselvam@eth.net India
SOURCE: Journal of Nutritional Biochemistry, (October 2002, 2002) Vol. 13, No. 10, pp. 619-624. print.
ISSN: 0955-2863.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Free radicals have been implicated in the development of many acute and chronic diseases and in conditions involving brain or neurological tissue. The primary genetic material is subjected to damage by endogenous and exogenous agents, which may lead to instability and transcriptional infidelity. In the present study, we evaluated the protective effect of DL-alpha-**lipoic acid**, a **metabolic antioxidant** on lipid peroxidation, protein carbonyl content in various brain regions of aged rats when compared to brain regions of young rats. DL-alpha-**lipoic acid** was administered intraperitoneally (100mg/kg body weight/day) to experimental rats. Nucleic acid and protein content were low whereas thiobarbituric acid reactive substances and protein carbonyl content (markers of free radical damage) were high in cortex, striatum, hippocampus and hypothalamus followed by cerebellum of aged rat brain. Lipoate administration for 14 days in aged rats increased the levels of nucleic acid and protein and **reduced** lipid peroxidation and protein oxidation. These results demonstrate that **lipoic acid** is a potent antioxidant for neuronal cells against age associated oxidative damage.

L22 ANSWER 9 OF 40 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2002129999 EMBASE
TITLE: Elimination of .bul.O(2)(-)/H(2)O(2) by .alpha.-**lipoic acid** mediates the recovery of basal EDRF/NO availability and the reversal of superoxide dismutase-induced relaxation in diabetic rat aorta.
AUTHOR: Koccak G.; Karasu C.
CORPORATE SOURCE: Dr. C. Karasu, Ankara University, Faculty of Pharmacy, Department of Pharmacology, Tandogan 06100 Ankara, Turkey. karasu@pharmacy.ankara.edu.tr
SOURCE: Diabetes, Obesity and Metabolism, (2002) 4/1 (69-74).
Refs: 28
ISSN: 1462-8902 CODEN: DOMEF6
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 003 Endocrinology
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Aim: The aims of this study were to ascertain the mechanism(s) of relaxant action of exogenous superoxide dismutase (SOD) in aortic rings obtained from 12-week, streptozotocin(STZ)-diabetic and age-matched control rats, and to examine the effects of .alpha.-**lipoic acid** (ALA) treatment (for 6 weeks, after 6 weeks of untreated diabetes) on SOD-induced relaxations. Materials and Methods: Thoracic aorta rings were

suspended to isolated tissue chamber, and the changes in isometric tension were recorded. Results: SOD produced a greater relaxation in untreated-diabetic rings compared with control rings. ALA treatment partially reversed SOD-induced relaxation in diabetic aorta. Pretreatment of rings with N(G)-nitro-L-arginine methyl ester (L-NAME, 100 .mu.M) inhibited SOD-induced relaxation. This effect of L-NAME was markedly observed in control and ALA-treated-diabetic rings compared with untreated-diabetic rings. SOD-induced relaxation was also inhibited by catalase (60 U/ml) in untreated-diabetic rings but not in ALA-treated-diabetic and control rings. Pretreatment with the cyclooxygenase inhibitor, indomethacin, or the catalase inhibitor, aminotriazole, had no effect on SOD-induced relaxation in any ring. Conclusion: Findings suggested that: (i) in normal physiological conditions, the relaxant effect of SOD is related to the inhibition of superoxide anion radicals ((.bul.)O(2)(-))-induced endothelium-derived relaxing factor/nitric oxide (EDRF/NO) destruction in the rat aorta; (ii) in diabetic state, excess (.bul.)O(2)(-)increasingly inhibits basal EDRF/NO, and the dismutation of excess (.bul.)O(2)(-)to H(2)O(2) is enhanced by exogenous SOD. H(2)O(2) a vasorelaxant molecule, which probably accounts for the increased responsiveness of diabetic rings to exogenous SOD; and (iii) the reversal effect of in vivo ALA treatment on SOD-induced relaxation in diabetic aorta is probably linked with the elimination of (.bul.)O(2)(-)/H(2)O(2), which mediates the recovery of basal EDRF/NO availability.

L22 ANSWER 10 OF 40 WPIDS (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 2001-514501 [56] WPIDS
DOC. NO. CPI: C2001-153732
TITLE: Composition comprising a combination of an oxidizing and/or **reducing** agent, a protein-denaturing agent, and a hapten, useful for treating neoplasms, tumors, and cancers.
DERWENT CLASS: B05 D16
INVENTOR(S): YU, B
PATENT ASSIGNEE(S): (YUBB-I) YU B
COUNTRY COUNT: 94
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2001052868	A1	20010726	(200156)*	EN	83

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW

AU 2001030977	A	20010731	(200171)		
US 2002044919	A1	20020418	(200228)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2001052868	A1	WO 2001-US1737	20010118
AU 2001030977	A	AU 2001-30977	20010118
US 2002044919	A1 Provisional	US 2000-177024P	20000119
		US 2001-765060	20010117

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2001030977 A	Based on	WO 200152868

PRIORITY APPLN. INFO: US 2000-177024P 20000119; US 2001-765060 20010117

AN 2001-514501 [56] WPIDS

AB WO 200152868 A UPAB: 20011001

NOVELTY - A composition (I) comprising a combination of an oxidizing or **reducing** agent, a protein-denaturing agent, and a hapten, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a kit comprising the combination (I);

(2) an article of manufacture comprising:

(a) packaging material;

(b) the combination above; and

(c) a label indicating that the article is for treating neoplasms; and

(3) a method for treating neoplasm in a mammal comprising in situ administration to the neoplasm of a mammal, a hapten and a coagulation agent or treatment that causes coagulation of the neoplasm (an autologous immune response is generated against the neoplasm).

ACTIVITY - Cytostatic.

31 advanced stage IV liver cancer patients were treated using the new combination. Prior to procedure, patients were given a mild sedative or painkiller. Patients were calmed thoroughly and were also monitored by modern medial imaging. With local anesthesia, percutaneous puncture was administered directly into the tumor using a spinal needle connected to a high-power syringe containing a combination of ethanol, H_2O_2, anticancer drug AraC (8 mg/ml) and hemotoxilin (5 mg/ml). Combination was injected directly into the tumor and distributed throughout the matrix of the whole tumor. Sonic imaging showed the stranger echo imaging which indicated the coagulation area.

Following coagulation lysis and tumor cell death monitored by sonic imaging, which showed liquefied echo, tumor started to shrink and disappear. Normal tissues grew replacing the tumor. The process was monitored by medical imaging systems. The amount of the ingredients of the combination injected into the tumor was determined by the diameter of tumors (cm) with 2 ml of the combination for each centimeter.

Procedure was repeated in 1-2 weeks. On average, each patient was treated with the injection for 3 times. No severe side effects for all the treated patients was observed, although some patients experienced tolerable pain the injection site while a few had light fever during the first week. All side effects disappeared in about 1 week. No serious complications happened in any cases.

MECHANISM OF ACTION - Gene therapy.

USE - The combination and the methods are useful for treating neoplasms, tumors, and cancers, including neoplasm or cancer of the e.g. adrenal gland, anus, auditory nerve, bile ducts, bladder, bone, brain, breast, bruccal, central nervous system, cervix, colon, ear, endometrium, esophagus, eye, eyelids, **fallopian** tube, gastrointestinal tract, head and neck, heart, kidney, larynx, liver, lung, or mandible.

The combination and methods may further be used in treating tumors of mesenchymal origin (e.g. connective tissue and derivatives, or endothelial and related tissues blood vessels), epithelial origin (stratified squamous carcinoma, or basal cells of skin or adenexa), and tumors derived from more than one neoplastic cell types derived from more than one germ layers.

The treatment may be used with radiation therapy, before surgery for

the pre-treatment of neoplasm for easier removal of the neoplastic mass and **reduces** the neoplasm metastasis rate, or with gene therapy.
Dwg.0/4

L22 ANSWER 11 OF 40 WPIDS (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 2001-328414 [34] WPIDS
DOC. NO. CPI: C2001-100693
TITLE: Treating neurobehavioral disorders comprises administering a composition comprising amino acid(s) and e.g. vitamins, neurotransmitter precursors, minerals, corticosteroids, enzyme inhibitors and/or immunological enhancers.
DERWENT CLASS: B05
INVENTOR(S): BECHTHOLD, J C; LILLY, T D
PATENT ASSIGNEE(S): (BECH-I) BECHTHOLD J C; (LILL-I) LILLY T D
COUNTRY COUNT: 91
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2001026642	A2	20010419	(200134)*	EN	91

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DZ EE ES FI GB GD GE GH GM HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW
AU 2000080038 A 20010423 (200147)

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2001026642	A2	WO 2000-US27894	20001006
AU 2000080038	A	AU 2000-80038	20001006

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 2000080038	A	Based on	WO 200126642

PRIORITY APPLN. INFO: US 2000-201043P 20000501; US 1999-158604P 19991008; US 1999-164049P 19991108; US 1999-166068P 19991117

AN 2001-328414 [34] WPIDS
AB WO 200126642 A UPAB: 20010620
NOVELTY - Treating a neurobehavioral disorder comprises administering intravenously a composition comprising amino acid(s), neurotransmitter precursors, vitamins, inhibitors of neurotransmitter degradation and/or immune function enhancers.

DETAILED DESCRIPTION - Treating a neurobehavioral disorder comprises administering intravenously a composition comprising amino acid(s), neurotransmitter precursors, vitamins, inhibitors of neurotransmitter degradation and/or immune function enhancers.

INDEPENDENT CLAIMS are included for:

(1) a sterile composition (I) for treating neurobehavioral disorders comprising:

(a) at least one amino acid;

(b) vitamin C; and

(c) an electrolyte solution.

(2) a sterile composition (II) for treating neurobehavioral disorders comprising:

(a) at least one amino acid;

(b) a corticosteroid; and

(c) an electrolyte solution;

(3) a sterile composition (III) for treating neurobehavioral disorders comprising:

(a) vitamin C;

(b) a corticosteroid; and

(c) an electrolyte solution;

(4) a sterile composition (IV) for treating neurobehavioral disorders comprising:

(a) at least one amino acid;

(b) an immune potentiating amount of gamma-globulin; and

(c) an electrolyte solution;

(5) a sterile composition (V) for treating neurobehavioral disorders comprising:

(a) at least one amino acid;

(b) an inhibitor of opioid peptide degradation; and

(c) an electrolyte solution;

(6) an oral composition (VI) for treating neurobehavioral disorders comprising:

(a) at least one amino acid; and

(b) a substance selected from Ginko Biloba, methylsulfonylmethane, phosphatidylserine, phosphatidylcholine, alpha **lipoic acid**, red ginseng root, L-aspartic acid, ephedrine, pancreatic enzymes, caffeine, theobromine, Hypericum perforatum extract, S-adenosyl methionine, dihydroxyacetate, DMAE, grape seed extract, betaine, prickly pear cactus extract, Gymnea sylvestre extract, nicotinamide adenine dinucleotide/hydrogen, cholecystokinin, Cyclo (His-Pro), corticotropin-releasing hormone, neuropeptide Y, galanin, monolaurin or fructo-oligosaccharides.

(7) a method for treating a neurobehavioral disorder comprising administering intravenously a sterile and isotonic composition comprising:

(a) vitamin C;

(b) a corticosteroid; and

(c) water;

(8) a method for treating a neurobehavioral disorder comprising:

(i) evaluating a neurobiological characteristic of the disorder; and

(ii) injecting the patient with an intravenous composition to treat the disorder; and

(9) a composition (VII) for treating a neurobehavioral disorder comprising:

(i) an inhibitor of opioid degradation; and

(ii) a substance selected from group (A) which comprises thymus extract, L-taurine, alpha-keto glutarate, lidocaine, L-glutathione, pyridoxal-5-phosphate, sodium ascorbate, oxytocin, L-glycine, L-leucine, gamma globulin, vitamin B complex, magnesium taurate, citric acid, chromium polynicotinate, chromium nicotinate, chromium picolynate, zinc chelate, calcium chelate, vitamin B-12, vitamin B-5, vitamin B-6, vitamin B-1, folic acid, L-taurine and balanced amino acid solution with electrolytes.

ACTIVITY - Anti-alcoholic, anti-depressant; nootropic; antismoking; antiaddictive; anxiolytic; tranquilizer; anorectic; neuroleptic; anticonvulsant; neuroprotective.

A 38 year old male suffering from sleep disorders, obsessive-compulsive disorder, anger and rage disorder, depression, drug and alcohol addiction, attention deficit hyperactivity disorder, neurally mediated hypotension, chronic fatigue syndrome, dyslexia and a history of

debilitating brain disorder for whom conventional therapies had minimal effect was given a number of infusion treatments culminating in an infusion comprising saline (500 ml), sodium ascorbate (25 mg), molybdenum (250 mg), magnesium (600 mg), vitamin E (500 IU), vitamin B1 + B complex (1 cc), manganese (2 cc), zinc (1 cc), selenium (2 cc), chromium (2 cc), calcium gluconate (7 cc), taurine (2 cc), copper solution (2 cc), adrenal cortical extract (5 cc) and vitamin A (1000000 IU). The subject noted a reduction in craving, fluid retention was improved and blood pressure stabilized. The subject also experienced an increased sense of calm and increased motivation, mood and energy.

MECHANISM OF ACTION - The components of the compositions are e.g. enzyme inhibitors (for inhibiting neurotransmitter degradation or opiate degradation), neurotransmitter precursors, insulin potentiators, dopamine receptor agonists, opiate receptor antagonists and ammonia scavengers.

USE - The compositions are useful for reducing symptoms associated with withdrawal, improving symptoms of drug and alcohol overuse and reducing or preventing cravings for addictive substances. The compositions and methods permit the brain to function more normally by supporting or increasing the function of deficient neurochemical pathways and can eliminate or decrease symptoms of withdrawal, craving or compulsion associated with addiction and other central neurobiological disorders. The methods are useful for treating neurobehavioral disorders and for diagnosing and/or evaluating underlying neurobehavioral disorders. The treatments are also useful for disorders involving carbohydrate addiction, weight gain and nicotine addiction. Neurobehaviors treatable by these methods and compositions include e.g. obesity, smoking, Tourette's Syndrome, ADHD (attention deficit hyperactivity disorders), ADD (attention deficit disorders), Schizoid/Avoidant Behavior, aggression, posttraumatic stress syndrome, alcoholism, drug addiction, obsessive compulsive disorders, learning disorders, reading problems, gambling, manic symptoms, phobias, panic attacks, oppositional defiant behavior, conduct disorder, sexual behavior disorders, schizoid disorders, somatization disorders, depression, sleep disorders, general anxiety disorders, stuttering, tic disorders, anger and violent behavior disorders as well as Huntington's chorea, amyotropic lateral sclerosis, environmental sensitivity, chemical injury syndrome and chronic fatigue syndrome.

ADVANTAGE - The compositions can minimize adverse effects of addiction and other neurobehavioral disorders in patients recovering from these disorders. The compositions can eliminate or decrease symptoms of withdrawal, craving or compulsion associated with addiction and other central neurobiological disorders and these effects can result in longer lasting improvements in symptoms, thus reducing the risk of relapse and also making it more likely that the patient will complete their course of treatment. The compositions are less expensive in comparison to the current costs of residential treatment for drug and alcohol addiction and costs incurred due to repeat therapy can be reduced.

Dwg.0/0

L22 ANSWER 12 OF 40 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.

ACCESSION NUMBER:	2001214174 EMBASE
TITLE:	Evidence for **reductive** activation of carcinogenic aristolochic acids by prostaglandin H synthase - (32)P-postlabeling analysis of DNA adduct formation.
AUTHOR:	Stiborova M.; Frei E.; Breuer A.; Wiessler M.; Schmeiser H.H.
CORPORATE SOURCE:	M. Stiborova, Faculty of Science, Department of Biochemistry, Charles University, Albertov 2030, 128 40 Prague 2, Czech Republic. stiborov@prfdec.natur.cuni.cz
SOURCE:	Mutation Research - Genetic Toxicology and Environmental Mutagenesis, (27 Jun 2001) 493/1-2 (149-160).

Refs: 52
ISSN: 1383-5718 CODEN: MRGMFI
PUBLISHER IDENT.: S 1383-5718(01)00171-1
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 022 Human Genetics
028 Urology and Nephrology
030 Pharmacology
037 Drug Literature Index
052 Toxicology
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Aristolochic acid (AA), a naturally occurring nephrotoxin and carcinogen, is implicated in an unique type of renal fibrosis, designated Chinese herbs nephropathy (CHN), which can develop to urothelial cancer. Understanding which enzymes are involved in AA activation and/or detoxication is important in the assessment of an individual susceptibility to this natural carcinogen. We examined the ability of prostaglandin H synthase (PHS) to activate AA to metabolites forming DNA adducts with the nuclease P1 and 1-butanol extraction enrichment procedure of the (32)P-postlabeling assay. PHS is a prominent enzyme in the kidney and urothelial tissues. Ram seminal vesicle (RSV) microsomes, which contain high levels of PHS, generated AA-DNA adduct patterns reproducing those found in renal tissues in CHN patients. 7-(Deoxyadenosin-N(6)-yl)aristolactam I, 7-(deoxyguanosin-N(2)-yl)aristolactam I and 7-(deoxyadenosin-N(6)-yl)aristolactam II were identified as AA-DNA adducts formed by AAI. Two adducts, 7-(deoxyguanosin-N(2)-yl)aristolactam II and 7-(deoxyadenosin-N(6)-yl)aristolactam II, were generated from AAII. According to the structures of the DNA adducts identified, **nitroreduction** is the crucial pathway in the metabolic activation of AA. The identity of PHS as the activating enzyme in RSV microsomes was proven with different cofactors and inhibitors. Only indomethacin, a selective inhibitor of PHS, significantly decreased the amount of adducts formed by RSV microsomes. The inhibitor of NADPH:CYP **reductase** (.alpha.-**lipoic acid**) and some selective inhibitors of cytochromes P450 (CYP) were not effective. Likewise, only cofactors of PHS, arachidonic acid and hydrogen peroxide, supported the DNA adduct formation of AAI and AAII, while NADPH and NADH were ineffective. These results demonstrate a key role of PHS in the activation pathway of AAI and AAII in the RSV microsomal system and were corroborated with the purified enzyme, namely ovine PHS-1. The results presented here are the first report demonstrating a **reductive** activation of nitroaromatic compounds by PHS-1. .COPYRGT. 2001 Elsevier Science B.V.

L22 ANSWER 13 OF 40 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2001222391 EMBASE
TITLE: Effect of .alpha.-**lipoic acid** on vascular responses and nociception in diabetic rats.
AUTHOR: Cameron N.E.; Jack A.M.; Cotter M.A.
CORPORATE SOURCE: N.E. Cameron, Department of Biomedical Sciences, University of Aberdeen, Institute of Medical Sciences, Foresterhill, Aberdeen AB25 2ZD, Scotland, United Kingdom. n.e.cameron@abdn.ac.uk
SOURCE: Free Radical Biology and Medicine, (1 Jul 2001) 31/1 (125-135).
Refs: 73
ISSN: 0891-5849 CODEN: FRBMEH
PUBLISHER IDENT.: S 0891-5849(01)00564-0
COUNTRY: United States
DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 006 Internal Medicine
008 Neurology and Neurosurgery
018 Cardiovascular Diseases and Cardiovascular Surgery
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Oxidative stress contributes to the vascular and neurological complications of diabetes mellitus. The aim was to evaluate the effects of treatment with the radical scavenger and transition metal chelator, .alpha.-**lipoic acid**, on endothelium-dependent relaxation of the mesenteric vasculature and on superior cervical ganglion blood flow in 8 week streptozotocin-induced diabetic rats. .alpha.-**Lipoic acid** effects on small nerve fiber-mediated nociception were also monitored. For the in vitro phenylephrine-precontracted mesenteric vascular bed, diabetes caused a 31% deficit in maximum endothelium-dependent relaxation to acetylcholine, and a 4-fold **reduction** in sensitivity. .alpha.-**Lipoic acid** gave 85% protection against these defects. Acetylcholine responses are mediated by nitric oxide and endothelium-derived hyperpolarizing factor: isolation of the latter by nitric oxide synthase blockade revealed a 74% diabetic deficit that was halved by .alpha.-**lipoic acid** . Superior cervical ganglion blood flow, 52% **reduced** by diabetes, was dose-dependently restored by .alpha.-**lipoic acid** (ED(50), 44 mg/kg/d). Diabetic rats exhibited mechanical and thermal hyperalgesia, which were abolished by .alpha.-**lipoic acid** treatment. Thus, diabetes impairs nitric oxide and endothelium-derived hyperpolarizing factor-mediated vasodilation. This contributes to **reduced** neural perfusion, and may be responsible for altered nociceptive function. The effect of .alpha.-**lipoic acid** strongly implicates oxidative stress in these events and suggests a potential therapeutic approach. .COPYRGT. 2001 Elsevier Science Inc.

L22 ANSWER 14 OF 40 WPIDS (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 2000-647335 [62] WPIDS
DOC. NO. CPI: C2000-195866
TITLE: New imino- or pyridyl-substituted **lipoic acid** derivatives, as nitrogen monoxide **synthase inhibitors** and antioxidant regenerating agents, useful e.g. for treating nervous system or cerebrovascular disorders or cancer.
DERWENT CLASS: B03 B05
INVENTOR(S): AUGUET, M; CHABRIER DE LASSAUNIERE, P; HARNETT, J; CHABRIER DE LASSAUNIERE, P E
PATENT ASSIGNEE(S): (SCRC) SCRAS SOC CONSEILS RECH & APPL SCI; (SCRC) SOC CONSEILS RECH & APPL SCI
COUNTRY COUNT: 88
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000059899	A1	20001012	(200062)*	FR	51

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZA ZW

FR 2791677	A1	20001006	(200062)		

AU 2000039709 A 20001023 (200107)
FR 2805537 A1 20010831 (200153)
EP 1169316 A1 20020109 (200205) FR
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI
KR 2001108444 A 20011207 (200236)
CN 1349523 A 20020515 (200260)
HU 2002000863 A2 20020828 (200264)
NZ 514888 A 20021220 (200309)

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2000059899	A1	WO 2000-FR814	20000331
FR 2791677	A1	FR 1999-4132	19990402
AU 2000039709	A	AU 2000-39709	20000331
FR 2805537	A1	FR 2000-2315	20000224
EP 1169316	A1	EP 2000-918930	20000331
		WO 2000-FR814	20000331
KR 2001108444	A	KR 2001-712615	20010929
CN 1349523	A	CN 2000-806977	20000331
HU 2002000863	A2	WO 2000-FR814	20000331
		HU 2002-863	20000331
NZ 514888	A	NZ 2000-514888	20000331
		WO 2000-FR814	20000331

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 2000039709	A	Based on	WO 200059899
EP 1169316	A1	Based on	WO 200059899
HU 2002000863	A2	Based on	WO 200059899
NZ 514888	A	Based on	WO 200059899

PRIORITY APPLN. INFO: FR 2000-2315 20000224; FR 1999-4132 19990402

AN 2000-647335 [62] WPIDS

AB WO 200059899 A UPAB: 20021105

NOVELTY - Imino- or pyridyl-substituted **lipoic acid** derivatives (Ia) or (Ib) are new.

DETAILED DESCRIPTION - Imino- or pyridyl-substituted **lipoic acid** derivatives of formulae (Ia) or (Ib) and their salts are new.

R1, R2 = H or D'; or

R1+ R2 = direct bond;

D' = 1-6C alkyl;

A = (CH2)mN(R3)CO(CH2)n, (CH2)mCON(R3)(CH2)n, (CH2)mN(R3)(CH2)n, (CH2)mCON(R3)(CH2)p-N(R4)(CH2)n, (CH2)mN(R3)CON(R4)(CH2)n or (CH2)m;

m, n = 0-6;

p = 2-6;

R3, R4 = H or D';

X = phenylene or phenylene-alkylene group of formula -C6H3(R5)-T-; or (CH2)q;

T = (CH2)i, T being attached to Y';

R5 = H, D', -(CH2)mQ or 5- or 6-membered heterocycle (containing O, N(R6) or S);

i, q = 0-6;

Q = halo, OH, CN, NH2, alkoxy, alkylthio, alkylamino or dialkylamino;

R6 = H, D' or the bond to the phenyl ring;
Y' = -N=C(B)-NH2 or R7-substituted 2-aminopyridinyl;
B' = D', NR8R9, SR10 or 5- or 6-membered aryl or 5-or 6-membered heteroaryl (containing 1-4 O, S and N, especially thiophene, furan, pyrrole or thiazole), both optionally substituted by D', 2-6C alkenyl or OD';
R8R9 = H or D'; or
NR8R9 = 5- or 6-membered non-aromatic heterocycle in which the ring members are CH2, NH, O or S;
R7, R10 = H or D'.
INDEPENDENT CLAIMS are included for the preparation of (Ia) or (Ib).
ACTIVITY - Neuroprotective; antiparkinsonian; analgesic; cerebroprotective; antiaddictive; antialcoholic; vasotropic; antiinfertility; nootropic; antiinflammatory; antidepressant; tranquilizer; neuroleptic; anticonvulsant; hypnotic; antimigraine; antithrombotic; antiemetic; antibacterial; immunosuppressive; cytostatic.
MECHANISM OF ACTION - Nitrogen monoxide (NO) **synthase inhibitor**; antioxidant regenerating agent. N-(4-(((2-Thienyl)(imino)methyl)-amino)-phenyl)-1,2-dithiolane-3-pentanamide (Iaa) had IC50 **less** than 4.5 micro M for inhibition of rat cerebellar neuronal constitutive NO synthase and EC50 **less** than 30 micro M for inhibiting the effects of glutamate-induced oxidative stress on cultured HT-22 cells.
USE - (I) are NO **synthase inhibitors** and/or antioxidant regenerating agents, useful for treating disorders involving NO and/or the redox state of thiol groups, specifically (i) central or peripheral nervous system disorders, especially Parkinson's disease, neurodegenerative disease, pain, cerebral or spinal cord trauma, addiction (e.g. to opioid drugs or alcohol), impotence and reproductive problems, cognitive disorders, encephalopathy, depression, anxiety, schizophrenia, epilepsy, sleep disorders and eating disorders, (ii) cerebrovascular disorders, especially migraine, cerebral infarction (of ischemic or hemorrhagic origin), ischemia or thrombosis or (iii) proliferative or inflammatory disease, emesis, septic shock, disorders caused by radioactive or solar irradiation or organ transplantation, autoimmune or autosomal disease or cancer (all claimed).
Dwg.0/0

L22 ANSWER 15 OF 40 WPIDS (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 2000-647288 [62] WPIDS
DOC. NO. CPI: C2000-195823
TITLE: Compositions containing nitrogen monoxide **synthase inhibitor** and dithiol having **metabolic antioxidant** activity, useful for treating cardio and cerebrovascular disorders, inflammatory disorders or auto-immune diseases.
DERWENT CLASS: B05
INVENTOR(S): AUGUET, M; CHABRIER DE LASSAUNIERE, P E; HARNETT, J; CHABRIER DE LASSAUNIERE, P
PATENT ASSIGNEE(S): (SCRC) SCRAS SOC CONSEILS RECH & APPL SCI
COUNTRY COUNT: 93
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000059448	A2	20001012	(200062)*	FR	15

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK

LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI
SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
FR 2791571 A1 20001006 (200062)
AU 2000036637 A 20001023 (200107)
EP 1169005 A2 20020109 (200205) FR
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RO SE SI
NO 2001004770 A 20011123 (200207)
JP 2002541077 W 20021203 (200309) 26

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2000059448	A2	WO 2000-FR812	20000331
FR 2791571	A1	FR 1999-4134	19990402
AU 2000036637	A	AU 2000-36637	20000331
EP 1169005	A2	EP 2000-915262	20000331
		WO 2000-FR812	20000331
NO 2001004770	A	WO 2000-FR812	20000331
		NO 2001-4770	20011001
JP 2002541077	W	JP 2000-609013	20000331
		WO 2000-FR812	20000331

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 2000036637	A	Based on	WO 200059448
EP 1169005	A2	Based on	WO 200059448
JP 2002541077	W	Based on	WO 200059448

PRIORITY APPLN. INFO: FR 1999-4134 19990402
AN 2000-647288 [62] WPIDS
AB WO 200059448 A UPAB: 20001130
NOVELTY - Pharmaceutical compositions contain:
(1) one or more substances that inhibit nitrogen monoxide (NO) synthase;
(2) one or more substances having **metabolic antioxidant** activity containing at least two thiol groups intervening in the redox status of thiol groups; and
(3) optionally a pharmaceutical carrier.
DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for a product containing the different substances in separated forms.
ACTIVITY - Antimigraine; hypotensive; cardiant; vasotropic; thrombolytic; antibacterial; immunosuppressive; antiemetic; cytostatic; neuroprotective; analgesic; antialcoholic; antidepressive; neuroleptic; anticonvulsant; anabolic; antiarteriosclerotic; ophthalmological; antipsoriatic; antirheumatic; antiarthritic; antiviral; anti-HIV; antidiabetic. Mice were injected intraperitoneally three times at 2 hourly intervals with 1-methyl-4-phenyl-1,2,3,6-**tetrahydropyridine** (**MPTP**) (15-20 mg/kg). This induced Parkinson-like symptoms resulting from degeneration of **dopaminergic** nigrostriatal neurones. The products under test were given orally 90 minutes before each **MPTP** injection and 90 minutes after the last one. The animal were sacrificed after 24 hours and level of **dopamine** in the striatum was measured. Group 1 received no test compounds, Group 2 received N-phenyl-2-thiophene carboximidamine alone (3 mg/kg), Group 3 received **reduced lipoic acid** alone (10 mg/kg), and Group 4 received N-phenyl-2-thiophene carboximidamine (3 mg/kg) plus

reduced lipoic acid (10 mg/kg). The **dopamine** levels were as follows: Group 1 - 3.24 ng/mg; Group 2 -3.77 ng/mg; Group 3 - 3.81 ng/mg; Group 4 - 5.21 ng/mg. These results show that only when both active materials are given is the neurotoxicity of **MPTP** effectively countered.

MECHANISM OF ACTION - NO **synthase inhibitors** and **metabolic antioxidants**.

USE - The compositions are useful for treating cardiovascular and cerebrovascular disorders such as migraine, hypertension, cardiac or cerebral infarctus, ischemias or thromboses, septic shock, radioactive irradiation, solar irradiation, organ transplants, central and peripheral nervous system disorders such as neurodegenerative diseases, pain, trauma, drug or alcohol dependence, erectile and reproductive disorders, cognitive disorders, depression, schizophrenia, epilepsy, or sleep or eating disorders, proliferative and inflammatory disorders such as cancers, atherosclerosis, cataracts, psoriasis, and rheumatoid arthritis, viral and auto-immune diseases such as lupus or AIDS, diabetes and its complications, autosomal genetic disorders, and any disorder characterized by production or dysfunctioning of nitrogen monoxide or implicating the redox status of thiols.

Dwg.0/0

L22 ANSWER 16 OF 40 MEDLINE DUPLICATE 2

ACCESSION NUMBER: 2000421445 MEDLINE
DOCUMENT NUMBER: 20399633 PubMed ID: 10945536
TITLE: Radiolabeled neuronal nitric oxide **synthase inhibitors**: synthesis, in vivo evaluation, and primate PET studies.
AUTHOR: Pomper M G; Musachio J L; Scheffel U; Macdonald J E; McCarthy D J; Reif D W; Villemagne V L; Yokoi F; Dannals R F; Wong D F
CORPORATE SOURCE: Department of Radiology, Johns Hopkins University School of Medicine, Baltimore, Maryland 21287-2182, USA.
SOURCE: JOURNAL OF NUCLEAR MEDICINE, (2000 Aug) 41 (8) 1417-25. Journal code: 0217410. ISSN: 0161-5505.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200009
ENTRY DATE: Entered STN: 20000915
Last Updated on STN: 20000915
Entered Medline: 20000905

AB The objectives of this study were to synthesize neuronal nitric oxide synthase (NOS-I)-selective imaging agents based on the 2 potent, selective inhibitors AR-R 17443 [N-(4-((2-((phenylmethyl) (methyl)-amino)ethyl) **phenyl)-2-thiophenecarboximidamide**)] and AR-R 18512 [(N(2-methyl-1,2,3,4-tetrahydroisoquinoline-7-yl)-2-thiophenecarboxim idamide)] in positron-emitting form and to evaluate regional brain uptake in rodents and primates. METHODS: [11C]AR-R 17443 and [11C]AR-R 18512 were produced by N-alkylation of the corresponding desmethyl precursors using [11C]iodomethane. Regional brain uptake of [11C]AR-R 17443 and [11C]AR-R 18512 was assayed in rats and NOS-I knockout mice, and PET was performed in baboons. Tracer kinetic modeling used a 2-compartment plasma and brain tissue model. RESULTS: Yields of [11C]AR-R 17443 and [11C]AR-R 18512 ranged from 8% to 16% at the end of synthesis, with specific activities of 50-178 GBq/micromol (1,350-4,800 Ci/mmol) at the end of synthesis. In rat cerebellum and cortex at 30 min after injection, [11C]AR-R 17443 showed 1.01 +/- 0.01 and 1.63 +/- 0.12 percentage injected dose per gram (%ID/g) uptake, respectively, whereas

[11C]AR-R 18512 showed 0.88 +/- 0.01 and 1.30 +/- 0.07 %ID/g uptake, respectively. Attempts to block tracer uptake by pretreatment with the NOS-I-selective inhibitor 7-nitroindazole or the corresponding unlabeled inhibitor (or desmethyl precursor to AR-R 17443 of similar potency) were unsuccessful. A small but significant (20%) decrease in cerebellar uptake of [11C]AR-R 18512 was present in NOS-I knockout mice compared with control mice. PET of [11C]AR-R 18512 in baboons with concurrent regional cerebral blood flow (rCBF) determination before and after administration of blocker showed dose-related decreases in cerebellar uptake that were greater than or equal to decreases in rCBF. Plasma metabolites accounted for 27% of total activity at 30 min after injection. Kinetic modeling of binding potentials revealed a distribution volume of 334 in cerebral blood that **dropped** 51% after blocker administration. CONCLUSION: Rodent studies for [11C]AR-R 17443 and [11C]AR-R 18512 showed little evidence of specific NOS-I binding. In baboons, we detected a higher uptake of [11C]AR-R 18512 in the cerebellum than in the cortex (approximately 5%, accounting for decreased rCBF because of blockade), indicating minimal specific binding. Analogs of higher affinity are likely required if this class of agents is to prove viable for PET.

L22 ANSWER 17 OF 40 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2000074700 EMBASE
TITLE: Drug treatment of Parkinson's disease. Time for phase II.
AUTHOR: Drukarch B.; Van Muiswinkel F.L.
CORPORATE SOURCE: Dr. B. Drukarch, Department of Neurology, Faculty of Medicine, Vrije Universiteit, vd. Boechorststr. 7, 1081 BT Amsterdam, Netherlands
SOURCE: Biochemical Pharmacology, (2000) 59/9 (1023-1031). Refs: 74
ISSN: 0006-2952 CODEN: BCPCA6
PUBLISHER IDENT.: S 0006-2952(99)00340-8
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 030 Pharmacology
037 Drug Literature Index
005 General Pathology and Pathological Anatomy
008 Neurology and Neurosurgery
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Parkinson's disease (PD) is a neurodegenerative syndrome for which at present no cure is available; therapy consists mainly of amelioration of the symptoms with L-Dopa and/or **dopamine** (DA) agonists. Development of an effective causal therapy should be focussed on preventing or at least retarding the neurodegenerative process underlying the disease. At the cellular level, PD is characterized by degeneration of neuromelanin-containing **dopaminergic** neurons in the substantia nigra. Neuromelanin formation is the outcome of a process generally known as DA autooxidation, a chain of oxidation reactions in which highly neurotoxic DA-quinones are produced. The level of these DA-quinones, as estimated by the occurrence of their cysteinyl conjugates, is reported to be increased in the Parkinsonian substantia nigra. Hence, stimulation of pathways implicated in the detoxication of DA-quinones in the brain may provide neuroprotection in PD. Besides their inactivation through non-enzymatic antioxidants such as ascorbic acid and glutathione, DA-quinones are efficiently inactivated enzymatically by NAD(P)H:quinone **oxidoreductase** (NQO) and glutathione transferase(s), both of which are expressed in the human substantia nigra. The activity of these enzymes, which belong to the group of phase II biotransformation enzymes, can be up-regulated by a large variety of compounds. These compounds, including dithiolethiones, phenolic anti-oxidants, and isothiocyanates,

have been shown to be active both in vitro and in vivo. Thus, considering the role of phase II biotransformation enzymes, in particular NQO and glutathione transferase(s), in the detoxication of DA-quinones, we propose that phase II enzyme inducers warrant evaluation on their neuroprotective potential in PD. Copyright (C) 2000 Elsevier Science Inc.

L22 ANSWER 18 OF 40 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 3

ACCESSION NUMBER: 2000:382757 BIOSIS
DOCUMENT NUMBER: PREV200000382757
TITLE: ARL 17477, a selective nitric oxide **synthase inhibitor**, with neuroprotective effects in animal models of global and focal cerebral ischaemia.
AUTHOR(S): O'Neill, Michael J. (1); Murray, Tracey K.; McCarty, Deborah R.; Hicks, Caroline A.; Dell, Colin P.; Patrick, Kelly E.; Ward, Mark A.; Osborne, David J.; Wiernicki, Todd R.; Roman, Carlos R.; Lodge, David; Fleisch, Jerome H.; Singh, JaiPal
CORPORATE SOURCE: (1) Lilly Research Centre, Eli Lilly and Co. Ltd., Erl Wood Manor, Windlesham, Surrey, GU20 6PH UK
SOURCE: Brain Research, (21 July) Vol. 871, No. 2, pp. 234-244. print.
ISSN: 0006-8993.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English

AB In the present studies, we have evaluated the effects of N-(4-(2-(((3-Chlorophenyl)methyl)amino)ethyl)**phenyl**)-**2-thiophenecarboximidamide** dihydrochloride (ARL 17477) on recombinant human neuronal NOS (nNOS) and endothelial NOS (eNOS). We then carried out pharmacokinetic studies and measured cortical nitric oxide synthase (NOS) inhibition to determine that the compound crossed the blood brain barrier. Finally, the compound was evaluated in a model of global ischaemia in the gerbil and two models of transient focal ischaemia in the rat. The IC50 values for ARL 17477 on human recombinant human nNOS and eNOS were 1 and 17 muM, respectively. ARL 17477 (50 mg/kg i.p.) produced a significant **reduction** in the ischaemia-induced hippocampal damage following global ischaemia when administered immediately post-occlusion, but failed to protect when administration was delayed until 30 min post-occlusion. In the endothelin-1 model of focal ischaemia, ARL 17477 (1 mg/kg i.v.) significantly attenuated the infarct volume when administered at either 0, 1 or 2 h post-endothelin-1 ($P<0.05$). In the intraluminal suture model, ARL 17477 at both 1 and 3 mg/kg i.v. failed to **reduce** the infarct volume measured at 1, 3 or 7 days post-occlusion. These results demonstrate that ARL 17477 protects against global ischaemia in gerbils and provides some **reduction** in infarct volume following transient middle cerebral artery occlusion in rats, indicating that nNOS inhibition may be a useful treatment of ischaemic conditions.

L22 ANSWER 19 OF 40 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 2000184188 EMBASE
TITLE: Inhibition of the cytokine-mediated inducible nitric oxide synthase expression in rat insulinoma cells by phenyl N-tert-butylnitrone.
AUTHOR: Tabatabaie T.; Graham K.L.; Vasquez A.M.; Floyd R.A.; Kotake Y.
CORPORATE SOURCE: T. Tabatabaie, Medical Research Foundation, Free Radical Biol./Aging Res. Prog., 825 N.E. 13th Street, Oklahoma City, OK 73104, United States. Tahereh-

Tabatabaie@omrf.ouhsc.edu
SOURCE: Nitric Oxide - Biology and Chemistry, (2000) 4/2 (157-167).
Refs: 52
ISSN: 1089-8603 CODEN: NIOXF5
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 003 Endocrinology
026 Immunology, Serology and Transplantation
029 Clinical Biochemistry
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Cytokines and nitric oxide (NO) have been implicated in the pathogenesis of insulin-dependent diabetes mellitus (IDDM). We have shown that the spin- trapping agent phenyl N-tert-butylnitrone (PBN) protects against streptozotocin (STZ)-induced IDDM in mice. In order to gain more insights into the mechanism(s) of the protective action of PBN against IDDM, we have investigated the effect of this compound on the cytokine-induced NO generation (measured as nitrite) in rat insulinoma RIN-5F cells. Our results demonstrate that PBN cotreatment prevents the generation of nitrite by RIN-5F cells induced by treatment with tumor necrosis factor-.alpha., interleukin 1.beta., and interferon-.gamma. in a dose-dependent fashion. The generation of NO as a result of cytokine treatment and the inhibitory effect of PBN were further confirmed by electron paramagnetic resonance spectroscopy. Aminoguanidine, a selective inhibitor of inducible nitric oxide synthase (iNOS), abolished the cytokine-induced nitrite generation whereas N-nitro-L-arginine, an inhibitor more selective for other NOS isoforms, was significantly **less** effective. Western and Northern analyses demonstrated that PBN inhibits the cytokine- mediated expression of iNOS at the transcriptional level. Cytokine-induced nitrite formation was also inhibited by the two antioxidant agents .alpha.-**lipoic acid** and N-acetylcysteine. These results indicate that PBN protects against IDDM at least in part by prevention of cytokine-induced NO generation by pancreatic .beta.-cells. (C) 2000 Academic Press.

L22 ANSWER 20 OF 40 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:157730 BIOSIS
DOCUMENT NUMBER: PREV200100157730
TITLE: **Lipoic acid**, a mitochondrial metabolite, counteracts the effect of neurotoxins on HT4 and HT22 hippocampal cell lines and mitochondrial decay in the brain of aged rats.
AUTHOR(S): Liu, J. (1); Amiri, N.; Hsu, J.; Ames, B.
CORPORATE SOURCE: (1) University of California, Berkeley, CA USA
SOURCE: Society for Neuroscience Abstracts, (2000) Vol. 26, No. 1-2, pp. Abstract No.-772.9. print.
Meeting Info.: 30th Annual Meeting of the Society of Neuroscience New Orleans, LA, USA November 04-09, 2000 Society for Neuroscience
. ISSN: 0190-5295.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Some toxins can cause neurotoxicity by the generation of oxidants with subsequent accumulation of oxidative damage. Oxidative damage can contribute to aging and to age-related neurodegeneration in Alzheimer's and Parkinson's disease. Therapeutic agents to prevent oxidative mitochondrial decay and neurotoxicity would be useful. The effects of **lipoic acid**, a strong antioxidant, on neurotoxin-induced

toxicity was studied with hippocampal cell lines HT4, and its subclone HT22. Dose-dependent cell injury in HT4 and HT22 cells, is caused by glutamate (an excitotoxin), hydrogen peroxide (a typical oxidant), homocysteic acid (a cysteine uptake inhibitor), diethyl maleate (a proxidant depleting intracellular glutathione), apomorphine (a memory impairing agent), 6-hydroxydopamine (an oxidant generator in the brain), and **MPTP** (a toxin causing Parkinson symptoms). The TD50 in HT22 was twice that in HT4, possibly due to the lack of ionotropic glutamate receptors in HT22 cells. **Lipoic acid** effectively protects against all of the toxins (except **MPTP**)-induced neurotoxicity. R-**Lipoic acid** when fed to old rats reverses age-related mitochondrial morphological changes in the brain as assayed by electron microscopy. We have also extended our previous work showing that R-**lipoic acid** increases ambulatory activity (Hagen et al. FASEB J. 13:411-8, 1999) and spatial memory (unpublished) in old rats. These results suggest that **lipoic acid** is an effective neuroprotective agent for ameliorating toxin-induced and age-associated neurodegeneration.

L22 ANSWER 21 OF 40 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1999328585 EMBASE
TITLE: BN 80933, a dual inhibitor of neuronal nitric oxide synthase and lipid peroxidation: A promising neuroprotective strategy.
AUTHOR: Chabrier P.-E.; Auguet M.; Spinnewy B.; Auvin S.; Cornet S.; Demerle-Pallardy C.; Guilmard-Favre C.; Marin J.-G.; Pignol B.; Gillard-Roubert V.; Roussillot- Charnet C.; Schulz J.; Viossat I.; Bigg D.; Moncada S.
CORPORATE SOURCE: P.-E. Chabrier, Beaufour-Ipsen Research Laboratories, Institut Henri Beaufour, 5 Avenue du Canada, 91966 Les Ulis Cedex, France. pierre-et.chabrier@beaufour-ipsen.com
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (1999) 96/19 (10824-10829). Refs: 40
ISSN: 0027-8424 CODEN: PNASA6
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 008 Neurology and Neurosurgery
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Nitric oxide (NO) and reactive oxygen species (ROS) act independently as well as cooperatively to induce neuronal death in acute neurological disorders. Inhibition of neuronal nitric oxide synthase (nNOS) and inhibition of lipid peroxidation induced by ROS have both been proposed as neuroprotective strategies in stroke and trauma. Recently, in our laboratory, the combination of the two strategies was found to be synergistic in **reducing** neuronal damage. Here, we report that BN 80933 [(S)-N- {4-[4-[(3,4-dihydro- 6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)carbonyl]-1- piperazinyl]**phenyl**}-2-**thiophenecarboximidamide**], a compound that combines potent antioxidant and selective nNOS inhibitory properties in vitro, affords remarkable neuronal protection in vivo. Intravenous administration of BN 80933 significantly **reduced** brain damage induced by head trauma in mice, global ischemia in gerbils, and transient focal ischemia in rats. Treatment with BN 80933 (0.3-10 mg/kg) significantly **reduced** infarct volume (>60% protection) and enhanced behavioral recovery in rats subjected to transient (2-h) middle cerebral artery occlusion and 48-h or 7-day reperfusion. Furthermore, treatment with BN 80933 commencing up to 8

h after the onset of ischemia resulted in a significant improvement of neurological outcome. All these results indicate that BN 80933 represents a class of potentially useful therapeutic agents for the treatment of stroke or trauma and possibly neurodegenerative disorders that involve both NO and ROS.

L22 ANSWER 22 OF 40 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 2000084683 MEDLINE
DOCUMENT NUMBER: 20084683 PubMed ID: 10619665
TITLE: Alpha-**lipoic acid** prevents 3,4-methylenedioxy-methamphetamine (MDMA)-induced neurotoxicity.
AUTHOR: Aguirre N; Barrionuevo M; Ramirez M J; Del Rio J; Lasheras B
CORPORATE SOURCE: Department of Pharmacology, School of Medicine, University of Navarra, Pamplona, Spain.
SOURCE: NEUROREPORT, (1999 Nov 26) 10 (17) 3675-80.
Journal code: 9100935. ISSN: 0959-4965.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200001
ENTRY DATE: Entered STN: 20000131
Last Updated on STN: 20000131
Entered Medline: 20000119

AB A single administration of 3,4-methylenedioxymethamphetamine (MDMA, 20 mg/kg, i.p.), induced significant hyperthermia in rats and **reduced** 5-hydroxytryptamine (5-HT) content and [3H]paroxetine-labeled 5-HT transporter density in the frontal cortex, striatum and hippocampus by 40-60% 1 week later. MDMA treatment also increased glial fibrillary acidic protein (GFAP) immunoreactivity in the hippocampus. Repeated administration of the **metabolic antioxidant** alpha-**lipoic acid** (100 mg/kg, i.p., b.i.d. for 2 consecutive days) 30 min prior to MDMA did not prevent the acute hyperthermia induced by the drug; however, it fully prevented the serotonergic deficits and the changes in the glial response induced by MDMA. These results further support the hypothesis that free radical formation is responsible for MDMA-induced neurotoxicity.

L22 ANSWER 23 OF 40 MEDLINE
ACCESSION NUMBER: 2001181681 MEDLINE
DOCUMENT NUMBER: 21121576 PubMed ID: 11228751
TITLE: Endogenous and new synthetic antioxidants for peroxynitrite: selective inhibitory effect of 5-methoxytryptamine and **lipoic acid** on tyrosine nitration by peroxynitrite.
AUTHOR: Nakagawa H; Sumiki E; Ikota N; Matsushima Y; Ozawa T
CORPORATE SOURCE: Bioregulation Research Group, National Institute of Radiological Sciences, Chiba 263, Japan.
SOURCE: ANTIOXIDANTS & REDOX SIGNALLING, (1999 Summer) 1 (2) 239-44.
Journal code: 100888899. ISSN: 1523-0864.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200103
ENTRY DATE: Entered STN: 20010404
Last Updated on STN: 20010404

Entered Medline: 20010329

AB The inhibitory effects of endogenous and synthetic compounds on the nitration and oxidation of L-tyrosine by peroxynitrite were examined. Nitration and oxidation activities of L-tyrosine by peroxynitrite were estimated by monitoring the formation of 3-nitrotyrosine and dityrosine with a high-performance liquid chromatography-ultraviolet (HPLC-UV)-fluorescence detector system. Glutathione and synthetic compounds ((2S,3R,4S)-N-ethylmercapto-3,4-dihydroxy-2-hydroxymethylpyrrolidine, L-N-dithiocarboxyproline) inhibited both the nitration and the oxidation reactions of L-tyrosine effectively. On the other hand, 5-methoxytryptamine and **lipoic acid** inhibited only the nitration reaction of L-tyrosine, and instead increased the oxidation reaction. It was assumed that 5-methoxytryptamine and **lipoic acid** reacted only with the nitrating species of peroxynitrite. This is the first report of a selective inhibitor for the nitrating reaction of peroxynitrite.

L22 ANSWER 24 OF 40 MEDLINE DUPLICATE 5
ACCESSION NUMBER: 1999180318 MEDLINE
DOCUMENT NUMBER: 99180318 PubMed ID: 10082281
TITLE: Attenuation of aminoglycoside-induced cochlear damage with the **metabolic antioxidant** alpha-**lipoic acid**.
AUTHOR: Conlon B J; Aran J M; Erre J P; Smith D W
CORPORATE SOURCE: The Hearing Research Laboratories, Division of Otolaryngology-Head and Neck Surgery, Duke University Medical Center, Durham, NC 27710, USA.
CONTRACT NUMBER: DC 01692 (NIDCD)
DC 02832 (NIDCD)
SOURCE: HEARING RESEARCH, (1999 Feb) 128 (1-2) 40-4.
Journal code: 7900445. ISSN: 0378-5955.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199904
ENTRY DATE: Entered STN: 19990511
Last Updated on STN: 19990511
Entered Medline: 19990427

AB Free radical generation is increasingly implicated in a variety of pathological processes, including drug toxicity. Recently, a number of studies have demonstrated the ability of gentamicin to facilitate the generation of radical species both in vivo and in vitro, which suggests that this process plays an important role in aminoglycoside-induced ototoxicity. Free radical scavengers are compounds capable of inactivating free radicals, thereby attenuating their tissue damaging capacity. In this study we have determined the ability of the powerful free radical scavenger alpha-**lipoic acid** (100 mg/kg/day) to attenuate the cochlear damage induced by a highly ototoxic regimen of the aminoglycoside amikacin (450 mg/kg/day, i.m.). Experiments were carried out on pigmented guinea pigs initially weighing 200-250 g. Changes in cochlear function were characterized as shifts in compound action potential (CAP) thresholds, estimated every 5 days, by use of chronic indwelling electrodes implanted at the round window, vertex, and contralateral mastoid. Results showed that animals receiving alpha-**lipoic acid** in combination with amikacin demonstrated a significantly **less** severe elevation in CAP thresholds compared with animals receiving amikacin alone ($P < 0.001$; t-test). These results provide further evidence of the recently reported intrinsic role of free radical generation in aminoglycoside ototoxicity, and highlight a

potential clinical therapeutic use of alpha-**lipoic acid** in the management of patients undergoing aminoglycoside treatment.

L22 ANSWER 25 OF 40 MEDLINE DUPLICATE 6
ACCESSION NUMBER: 1998234064 MEDLINE
DOCUMENT NUMBER: 98234064 PubMed ID: 9573120
TITLE: Effects of the antioxidant alpha-**lipoic acid** on human umbilical vein endothelial cells infected with Rickettsia rickettsii.
AUTHOR: Eremeeva M E; Silverman D J
CORPORATE SOURCE: School of Medicine, University of Maryland, Baltimore 21201, USA.
CONTRACT NUMBER: AI 17416 (NIAID)
SOURCE: INFECTION AND IMMUNITY, (1998 May) 66 (5) 2290-9. Journal code: 0246127. ISSN: 0019-9567.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199805
ENTRY DATE: Entered STN: 19980520
Last Updated on STN: 19980520
Entered Medline: 19980514

AB Rickettsia rickettsii infection of endothelial cells is manifested in very distinctive changes in cell morphology, consisting of extensive dilatation of the membranes of the endoplasmic reticulum and outer nuclear envelope and blebbing of the plasma membrane, as seen by transmission electron microscopy (D. J. Silverman, Infect. Immun. 44:545-553, 1984). These changes in cellular architecture are thought to be due to oxidant-mediated cell injury, since their occurrence correlates with dramatic alterations in cellular metabolism, particularly with regard to antioxidant systems. In this study, it was shown that R. rickettsii infection of human umbilical vein endothelial cells resulted in a significant depletion of intracellular **reduced** glutathione (thiol) content at 72 and 96 h and decreased glutathione peroxidase activity at 72 h postinfection. Infected cells displayed a dramatic increase in the concentration of intracellular peroxides by 72 h. Supplementation of the cell culture medium with 100, 200, or 500 microM alpha-**lipoic acid**, a **metabolic antioxidant**, after inoculation with R. rickettsii restored the intracellular levels of thiols and glutathione peroxidase and **reduced** the intracellular peroxide levels in infected cells. These effects were dose dependent. Treated infected monolayers maintained better viability at 96 h after inoculation with R. rickettsii than did untreated infected cells. Moreover, supplementation of the cell culture medium with 100 microM alpha-**lipoic acid** for 72 h after infection prevented the occurrence of morphological changes in the infected cells. The presence of 100 or 200 microM alpha-**lipoic acid** did not influence rickettsial growth in endothelial cells, nor did it affect the ability of R. rickettsii to form lytic plaques in Vero cells. Treatment with 500 microM alpha-**lipoic acid** decreased by 50% both the number and size of lytic plaques in Vero cells, and it also decreased the recovery of viable rickettsiae from endothelial cells. However, under all treatment conditions, a significant number of rickettsiae could be detected microscopically. Furthermore, the rickettsiae apparently retained their capacity for intracellular movement, since they possessed long polymerized actin tails after 72 and 96 h of treatment **regardless** of the concentration of alpha-**lipoic acid** used. Since alpha-**lipoic acid** does not seem to exhibit direct antirickettsial activity except with long-term exposure at very high

concentrations, the mechanism of its protective activity for endothelial cells infected with rickettsiae may involve complex changes in cellular metabolism that only indirectly affect rickettsiae.

L22 ANSWER 26 OF 40 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1998410691 EMBASE
TITLE: [Pathogenesis of diabetic neuropathy].
PATHOGENESE DER DIABETISCHEN NEUROPATHIE.
AUTHOR: Ziegler D.
CORPORATE SOURCE: Dr. D. Ziegler, Diabetes-Forschungsinstitut, Heinrich-Heine-Universitat, Klinische Abteilung, Auf'm Hennekamp 65, 40225 Dusseldorf, Germany
SOURCE: Diabetes und Stoffwechsel, (20 Nov 1998) 7/6 (251-266).
Refs: 134
ISSN: 0942-0037 CODEN: DISTF5
COUNTRY: Germany
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 006 Internal Medicine
008 Neurology and Neurosurgery
037 Drug Literature Index
LANGUAGE: German
SUMMARY LANGUAGE: English; German

AB Recent experimental studies suggest a multifactorial pathogenesis of diabetic neuropathy. Most data have been generated in the diabetic rat model, on the basis of which two approaches have been chosen to contribute to the clarification of the pathogenesis of diabetic neuropathy. Firstly, it has been attempted to characterize the pathophysiological, pathobiochemical, and structural abnormalities that result in experimental diabetic neuropathy. Secondly, specific therapeutic interventions have been employed to prevent the development of these alterations, to halt their progression, or to induce their regression despite concomitant hyperglycaemia. At present, the following six pathogenetic mechanisms are being discussed which, however, in contrast to previous years, are no longer regarded as separate hypotheses but in the first place as a complex interplay with multiple interactions between metabolic and vascular factors: 1. Increased flux through the polyol pathway that leads to accumulation of sorbitol and Fructose, depletion of myo- inositol, **reduction** in Na+-K+-ATPase activity and alterations in the expression of several isoenzymes of protein kinase C (PKC); 2. Disturbances in n-6 essential fatty acid and prostaglandin metabolism which result in alterations of nerve membrane structure and microvascular and haemorrheologic abnormalities; 3. Endoneurial microvascular deficits with subsequent ischaemia and hypoxia as well as generation of reactive oxygen species (oxidative stress) and the so called oil, administration of antioxidants (.alpha.- **lipoic acid**) to **reduce** the enhanced formation of reactive oxygen species that induce increased oxidative stress, improvement in endoneurial blood flow and resulting hypoxia by vasodilating agents such as ACE inhibitors and prostaglandin analogues, neurotrophic support by administration of NGF, inhibition of non-enzymatic glycation and formation of AGEs by aminoguanidine and immunosuppressive treatment. Since in the foreseeable future (near-)normoglycaemia will not be achievable in the majority of diabetic patients, the advantage of the aforementioned treatment approaches is that they may exert their effects despite prevailing hyperglycaemia. In future, combinations of certain drugs that produce synergistic effects could be used as therapeutic options.

L22 ANSWER 27 OF 40 MEDLINE DUPLICATE 7
ACCESSION NUMBER: 1998269448 MEDLINE
DOCUMENT NUMBER: 98269448 PubMed ID: 9606603

TITLE: alpha-**Lipoic acid**: a **metabolic antioxidant** which regulates NF-kappa B signal transduction and protects against oxidative injury.
AUTHOR: Packer L
CORPORATE SOURCE: Department of Molecular and Cell Biology, University of California, Berkeley 94720-3200, USA.
SOURCE: DRUG METABOLISM REVIEWS, (1998 May) 30 (2) 245-75. Ref: 113
Journal code: 0322067. ISSN: 0360-2532.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199807
ENTRY DATE: Entered STN: 19980731
Last Updated on STN: 19980731
Entered Medline: 19980723

AB Although the metabolic role of alpha-**lipoic acid** has been known for over 40 years, it is only recently that its effects when supplied exogenously have become known. Exogenous alpha-**lipoic acid** is **reduced** intracellularly by at least two and possibly three enzymes, and through the actions of its **reduced** form, it influences a number of cell process. These include direct radical scavenging, recycling of other antioxidants, accelerating GSH synthesis, and modulating transcription factor activity, especially that of NF-kappa B (Fig. 12). These mechanisms may account for the sometimes dramatic effects of alpha-**lipoic acid** in oxidative stress conditions (e.g., brain ischemia-reperfusion), and point the way toward its therapeutic use.

L22 ANSWER 28 OF 40 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 97120719 EMBASE
DOCUMENT NUMBER: 1997120719
TITLE: Regulation of cellular thiols in human lymphocytes by .alpha.-**lipoic acid**: A flow cytometric analysis.
AUTHOR: Sen C.K.; Roy S.; Han D.; Packer L.
CORPORATE SOURCE: Dr. C.K. Sen, 251 Life Science Addition, Department of Molecular/Cell Biology, University of California, Berkeley, CA 94720-3200, United States
SOURCE: Free Radical Biology and Medicine, (1997) 22/7 (1241-1257). Refs: 62
ISSN: 0891-5849 CODEN: FRBMEH
PUBLISHER IDENT.: S 0891-5849(96)00552-7
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Modulation of cellular thiols is an effective therapeutic strategy, particularly in the treatment of AIDS. **Lipoic acid**, a **metabolic antioxidant**, functions as a redox modulator and has proven clinically beneficial effects. It is also used as a dietary supplement. We utilized the specific capabilities of N-ethylmaleimide to block total cellular thiols, phenylarsine oxide to block vicinal dithiols, and buthionine sulfoximine to deplete cellular GSH to flow cytometrically investigate how these thiol pools are influenced by exogenous lipoate

treatment. Low concentrations of lipoate and its analogue lipoamide increased Jurkat cell GSH in a dose-dependent manner between 10 (25 .mu.M for lipoamide) to 100 .mu.M. This was also observed in mitogenically stimulated peripheral blood lymphocytes (PBL). Studies with Jurkat cells and its Wurzburg subclone showed that lipoate dependent increase in cellular GSH was similar in CD4+ and - cells. Chronic (16 week) exposure of cells to lipoate resulted in further increase of total cellular thiols, vicinal dithiols, and GSH. High concentration (2 and 5 mM) of lipoate exhibited cell shrinkage, thiol depletion, and DNA fragmentation effects. Based on similar effects of octanoic acid, the cytotoxic effects of lipoate at high concentration could be attributed to its fatty acid structure. In certain diseases such as AIDS and cancer, elevated plasma glutamate lowers cellular GSH by inhibiting cystine uptake. Low concentrations of lipoate and lipoamide were able to bypass the adverse effect of elevated extracellular glutamate. A heterogeneity in the thiol status of PBL was observed. Lipoate, lipoamide, or N-acetylcysteine corrected the deficient thiol status of cell subpopulations. Hence, the favorable effects of low concentrations of lipoate treatment appears clinically relevant.

L22 ANSWER 29 OF 40 MEDLINE DUPLICATE 8
ACCESSION NUMBER: 97117078 MEDLINE
DOCUMENT NUMBER: 97117078 PubMed ID: 8958163
TITLE: Neuroprotection by the **metabolic antioxidant** alpha-**lipoic acid.**
AUTHOR: Packer L; Tritschler H J; Wessel K
CORPORATE SOURCE: Department of Molecular and Cell Biology, University of California, Berkeley 94720-3200, USA.
SOURCE: FREE RADICAL BIOLOGY AND MEDICINE, (1997) 22 (1-2) 359-78. Ref: 215
Journal code: 8709159. ISSN: 0891-5849.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199704
ENTRY DATE: Entered STN: 19970422
Last Updated on STN: 19970422
Entered Medline: 19970410

AB Reactive oxygen species are thought to be involved in a number of types of acute and chronic pathologic conditions in the brain and neural tissue. The **metabolic antioxidant** alpha-lipoate (thioctic acid, 1, 2-dithiolane-3-pentanoic acid; 1, 2-dithiolane-3 valeric acid; and 6, 8-dithiooctanoic acid) is a low molecular weight substance that is absorbed from the diet and crosses the blood-brain barrier. alpha-Lipoate is taken up and **reduced** in cells and tissues to dihydrolipoate, which is also exported to the extracellular medium; hence, protection is afforded to both intracellular and extracellular environments. Both alpha-lipoate and especially dihydrolipoate have been shown to be potent antioxidants, to regenerate through redox cycling other antioxidants like vitamin C and vitamin E, and to raise intracellular glutathione levels. Thus, it would seem an ideal substance in the treatment of oxidative brain and neural disorders involving free radical processes. Examination of current research reveals protective effects of these compounds in cerebral ischemia-reperfusion, excitotoxic amino acid brain injury, mitochondrial dysfunction, diabetes and diabetic neuropathy, inborn errors of metabolism, and other causes of acute or chronic damage to brain or neural tissue. Very few neuropharmacological intervention strategies are

currently available for the treatment of stroke and numerous other brain disorders involving free radical injury. We propose that the various **metabolic antioxidant** properties of alpha-lipoate relate to its possible therapeutic roles in a variety of brain and neuronal tissue pathologies: thiols are central to antioxidant defense in brain and other tissues. The most important thiol antioxidant, glutathione, cannot be directly administered, whereas alpha-**lipoic acid** can. In vitro, animal, and preliminary human studies indicate that alpha-lipoate may be effective in numerous neurodegenerative disorders.

L22 ANSWER 30 OF 40 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1998009982 EMBASE
TITLE: Free radical scavengers protect dopaminergic cell lines from apoptosis induced by complex I inhibitors.
AUTHOR: Seaton T.A.; Cooper J.M.; Schapira A.H.V.
CORPORATE SOURCE: A.H.V. Schapira, Univ. Dept. of Clinical Neuroscience, Royal Free Hosp. School of Medicine, Rowland Hill Street, London NW3 2PF, United Kingdom. schapira@rfhsm.ac.uk
SOURCE: Brain Research, (1997) 777/1-2 (110-118).
Refs: 70
ISSN: 0006-8993 CODEN: BRREAP
PUBLISHER IDENT.: S 0006-8993(97)01034-2
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 008 Neurology and Neurosurgery
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The cause of dopaminergic neurodegeneration in Parkinson's disease remains unclear, but may involve both oxidative stress and mitochondrial complex I inhibition. We have demonstrated that complex I inhibitors, including rotenone, MPP+, isoquinoline and tetrahydroisoquinoline, induce apoptosis in PC12 and SK-N-MC dopaminergic cell lines which was decreased by pretreatment with N-acetylcysteine, TEMPO, **dihydrolipoic acid** or pyrrolidine dithiocarbamate. These results indicate that the pathway leading to apoptosis following complex I inhibition involves free radical generation. The free radical generation may result directly from inhibition of the mitochondrial respiratory chain or indirectly during the apoptotic process itself. This has important implications for our understanding of the relationship between complex I deficiency and oxidative stress and neurodegeneration in Parkinson's disease.

L22 ANSWER 31 OF 40 MEDLINE
ACCESSION NUMBER: 97051066 MEDLINE
DOCUMENT NUMBER: 97051066 PubMed ID: 8895805
TITLE: Alpha-**lipoic acid**: a **metabolic antioxidant** and potential redox modulator of transcription.
AUTHOR: Packer L; Roy S; Sen C K
CORPORATE SOURCE: Department of Molecular and Cell Biology, University of California at Berkeley 94720, USA.
SOURCE: ADVANCES IN PHARMACOLOGY, (1997) 38 79-101. Ref: 102
Journal code: 9015397. ISSN: 1054-3589.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199702
ENTRY DATE: Entered STN: 19970219

Last Updated on STN: 19970219
Entered Medline: 19970204

L22 ANSWER 32 OF 40 MEDLINE
ACCESSION NUMBER: 97059985 MEDLINE
DOCUMENT NUMBER: 97059985 PubMed ID: 8904306
TITLE: Alpha-**lipoic acid**: the **metabolic antioxidant**.
AUTHOR: Packer L; Tritschler H J
SOURCE: FREE RADICAL BIOLOGY AND MEDICINE, (1996) 20 (4) 625-6.
Journal code: 8709159. ISSN: 0891-5849.
PUB. COUNTRY: United States
DOCUMENT TYPE: Letter
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199704
ENTRY DATE: Entered STN: 19970414
Last Updated on STN: 19970414
Entered Medline: 19970401

L22 ANSWER 33 OF 40 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 96364277 EMBASE
DOCUMENT NUMBER: 1996364277
TITLE: Neuroprotection by the **metabolic antioxidant** .alpha.-**lipoic acid**
.
AUTHOR: Packer L.; Tritschler H.J.; Wessel K.
CORPORATE SOURCE: Department of Molecular/Cell Biology, 251 Life Sciences Addition, University of California,Berkeley, CA 94720-3200, United States
SOURCE: Free Radical Biology and Medicine, (1996) 22/1-2 (359-378). ISSN: 0891-5849 CODEN: FRBMEH
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 008 Neurology and Neurosurgery
021 Developmental Biology and Teratology
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Reactive oxygen species are thought to be involved in a number of types of acute and chronic pathologic conditions in the brain and neural tissue. The **metabolic antioxidant** .alpha.-lipoate (thioctic acid, 1, 2-dithiolane-3- pentanoic acid; 1, 2-dithiolane-3 valeric acid; and 6,8-dithiooctanoic acid) is a low molecular weight substance that is absorbed from the diet and crosses the blood-brain barrier. .alpha.-Lipoate is taken up and **reduced** in cells and tissues to dihydrolipoate, which is also exported to the extracellular medium; hence, protection is afforded to both intracellular and extracellular environments. Both .alpha.-lipoate and especially dihydrolipoate have been shown to be potent antioxidants, to regenerate through redox cycling other antioxidants like vitamin C and vitamin E, and to raise intracellular glutathione levels. Thus, it would seem an ideal substance in the treatment of oxidative brain and neural disorders involving free radical processes. Examination of current research reveals protective effects of these compounds in cerebral ischemia-reperfusion, excitotoxic amino acid brain injury, mitochondrial dysfunction, diabetes and diabetic neuropathy, inborn errors of metabolism, and other causes of acute or chronic damage to brain or neural tissue. Very few neuropharmacological intervention strategies are currently available for the treatment of stroke and numerous other brain disorders involving free radical injury. We propose that the various **metabolic antioxidant** properties of

.alpha.-lipoate relate to its possible therapeutic roles in a variety of brain and neuronal tissue pathologies: thiols are central to antioxidant defense in brain and other tissues. The most important thiol antioxidant, glutathione, cannot be directly administered, whereas .alpha.-**lipoic acid** can. In vitro, animal, and preliminary human studies indicate that .alpha.- lipoate may be effective in numerous neurodegenerative disorders.

L22 ANSWER 34 OF 40 MEDLINE
ACCESSION NUMBER: 96293920 MEDLINE
DOCUMENT NUMBER: 96293920 PubMed ID: 8731015
TITLE: Catecholamines enhance dihydrolipoamide dehydrogenase inactivation by the copper Fenton system. Enzyme protection by copper chelators.
AUTHOR: Correa J G; Stoppani A O
CORPORATE SOURCE: Bioenergetics Research Centre, School of Medicine (University of Buenos Aires), Paraguay, Argentina.
SOURCE: FREE RADICAL RESEARCH, (1996) 24 (4) 311-22.
Journal code: 9423872. ISSN: 1071-5762.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199609
ENTRY DATE: Entered STN: 19961008
Last Updated on STN: 20000303
Entered Medline: 19960920

AB Catecholamines (CAs: epinephrine, norepinephrine, **dopamine**, L-DOPA, 6-**hydroxydopamine**) and o-diphenols (DOPAC and catechol) enhanced dihydrolipoamide dehydrogenase (LADH) inactivation by Cu(II)/H2O2 (Cu-Fenton system). The inhibition of LADH activity correlated with Cu(II), H2O2 and CA concentrations. Similar inhibitions were obtained with the assayed CAs and o-diphenols. CAs enhanced HO. radical production by Cu(II)/H2O2, as demonstrated by benzoate hydroxylation and deoxyribose oxidation; LADH counteracted the pro-oxidant effect of CAs by scavenging hydroxyl radicals. Captopril, dihydrolipoamide, **dihydrolipoic acid**, DL-dithiothreitol, GSSG, trypanothione and histidine effectively preserved LADH from oxidative damage, whereas N-acetylcysteine, N-(2-mercaptopropionylglycine) and lipoamide were **less** effective protectors. Catalase (though neither bovine serum albumin nor superoxide dismutase) protected LADH against the Cu(II)/H2O2/CAs systems. Denatured catalase protected **less** than the native enzyme, its action possibly depending on Cu-binding. LADH increased and Captopril inhibited epinephrine oxidation by Cu(II)/H2O2 and Cu(II). The summarized evidence supports the following steps for LADH inactivation: (1) **reduction** of LADH linked-Cu(II) to Cu(I) by CAs; (2) production of HO. from H2O2 by LADH-linked Cu(I) (Haber-Weiss reaction) and (3) oxidation of aminoacid residues at the enzyme active site by site-specifically generated HO. radicals. Hydrogen peroxide formation from CAs autoxidation may contribute to LADH inactivation.

L22 ANSWER 35 OF 40 MEDLINE
ACCESSION NUMBER: 97044415 MEDLINE
DOCUMENT NUMBER: 97044415 PubMed ID: 8889486
TITLE: 2D NMR of the **metabolic antioxidant dihydrolipoic acid** and its derivatives.
AUTHOR: Schepkin V; Kawabata T; Tritschler H J; Packer L
CORPORATE SOURCE: Department of Molecular & Cell Biology, University of California, Berkely 94720-3200, USA.
SOURCE: FREE RADICAL RESEARCH, (1996 Sep) 25 (3) 195-205.

Journal code: 9423872. ISSN: 1071-5762.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199702
ENTRY DATE: Entered STN: 19970219
Last Updated on STN: 19970219
Entered Medline: 19970205

AB **Dihydroplipoate** and lipoate are physiological thiols which in addition to their coenzyme functions exhibit antioxidant activity. For NMR investigations of their protective mechanism in biological and model systems it is very important to know the full assignment of proton and carbon spectra of these molecules in water (D2O). An unambiguous assignment of proton and carbon NMR spectra has been made for dihydrolipoate and its short chain derivatives bisnor- and tetranor-**lipoic acid** in D2O and CDCl3 solutions using 2D NMR methods. Oxidation of **dihydrolipoic acid** produces substantial electron density deshielding of the carbons nearest to the SH groups with the largest shift found at the inner SH group (17.79 ppm in D2O, 16.93 in CDCl3) and almost no changes in the tail portion of the molecule. However, bisnor-**dihydrolipoic acid** and especially tetranor-**dihydrolipoic acid** have more carbon deshielding near the outer SH group of the molecule which correlates with their known diminished ion chelating activity. Moreover, the proton triplet at position 2 of **lipoic acid** has strong pH dependence (pK = 4.58) due to the close proximity to the carboxylic group and this feature may be used for monitoring pH.

L22 ANSWER 36 OF 40 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 95199032 EMBASE
DOCUMENT NUMBER: 1995199032
TITLE: Neuroprotective therapeutic strategies. Comparison of experimental and clinical results.
AUTHOR: Gerlach M.; Riederer P.; Youdim M.B.H.
CORPORATE SOURCE: Klinische Neurochemie, Universitats-Nervenklinik, Fuchsleinstrasse 15,D-97080 Wurzburg, Germany
SOURCE: Biochemical Pharmacology, (1995) 50/1 (1-16). ISSN: 0006-2952 CODEN: BCPCA6
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
008 Neurology and Neurosurgery
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English

L22 ANSWER 37 OF 40 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1995:136926 BIOSIS
DOCUMENT NUMBER: PREV199598151226
TITLE: Influence of N-methyl-4-phenyl-1,2,3,6,-tetrahydropyridine, **lipoic acid** and L-deprenyl on the interplay between cellular redox systems.
AUTHOR(S): Goetz, M. E. (1); Dirr, A.; Gsell, W.; Burger, R.; Janetzky, B.; Freyberger, A.; Reichmann, H.; Rausch, W.-D.; Riederer, P.
CORPORATE SOURCE: (1) Dep. Psychiatry, Div. Clin. Neurochem., Univ. Wuerzburg, Fuechsleinstr. 15, D-97080 Wuerzburg Germany
SOURCE: Riederer, P. [Editor]; Fritze, J. [Editor]; Youdim, M. B.

H. [Editor]. Journal of Neural Transmission Supplement, (1994) Vol. 43, pp. 145-162. Journal of Neural Transmission Supplement; Neuroprotection in neurodegeneration.
Publisher: Springer-Verlag Postfach 89, Sachsenplatz 4-6, Vienna, Austria.
Meeting Info.: International Symposium Wuerzburg, Germany April 21-24, 1993
ISSN: 0303-6995. ISBN: 3-211-82542-8, 0-387-82542-8.
DOCUMENT TYPE: Book; Conference
LANGUAGE: English

L22 ANSWER 38 OF 40 MEDLINE DUPLICATE 9
ACCESSION NUMBER: 94229137 MEDLINE
DOCUMENT NUMBER: 94229137 PubMed ID: 8174612
TITLE: Effect of **lipoic acid** on redox state of coenzyme Q in mice treated with 1-methyl-4-phenyl-1,2,3,6-**tetrahydropyridine** and diethyldithiocarbamate.
AUTHOR: Gotz M E; Dirr A; Burger R; Janetzky B; Weinmuller M; Chan W W; Chen S C; Reichmann H; Rausch W D; Riederer P
CORPORATE SOURCE: Department of Psychiatry, University of Wurzburg, FRG.
SOURCE: EUROPEAN JOURNAL OF PHARMACOLOGY, (1994 Feb 15) 266 (3) 291-300.
Journal code: 1254354. ISSN: 0014-2999.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199406
ENTRY DATE: Entered STN: 19940620
Last Updated on STN: 19940620
Entered Medline: 19940603

AB We investigated the effects of a combined treatment of male C57Bl/6 mice with diethyldithiocarbamate and 1-methyl-4-phenyl-1,2,3,6-**tetrahydropyridine** (**MPTP**) in the absence or presence of different forms of **lipoic acid** (Thioctacid TR; commonly used for treatment of diabetic polyneuropathies) on levels and redox states of alpha-tocopherol and coenzyme Q in vivo and on activities of various enzymes of energy metabolism ex vivo. Treatment of mice with diethyldithiocarbamate plus **MPTP** resulted in a decrease in **dopamine** (67%) and its major metabolites dihydroxyphenylacetic acid (38%) and homovanillic acid (37%) in striatum. alpha-Tocopherol levels were unaltered in striatum; however, the **reduced** forms of coenzyme Q were decreased in frontal cortex and hippocampus following diethyldithiocarbamate plus **MPTP**. In frontal cortex activity of NADH dehydrogenase was significantly inhibited by diethyldithiocarbamate plus **MPTP** ex vivo, suggesting that the neurotoxic metabolite of **MPTP**, 1-methyl-4-phenylpyridinium ion, is acting in brain regions other than striatum as well. **Lipoic acid**, administered 6 times, each at 90 min prior to **MPTP**, could not restore **dopamine** in striatum but in contrast maintained a normal ratio of the **reduced** form to the oxidized form of coenzyme Q, suggesting an interaction of **lipoic acid** with energy metabolism which seems, however, not only to be due to an activation of pyruvate dehydrogenase.

L22 ANSWER 39 OF 40 MEDLINE DUPLICATE 10
ACCESSION NUMBER: 95190483 MEDLINE
DOCUMENT NUMBER: 95190483 PubMed ID: 7884397
TITLE: Influence of N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, **lipoic acid** and L-deprenyl on the

interplay between cellular redox systems.
AUTHOR: Gotz M E; Dirr A; Gsell W; Burger R; Janetzky B; Freyberger A; Reichmann H; Rausch W D; Riederer P
CORPORATE SOURCE: Department of Psychiatry, University of Wurzburg, Federal Republic of Germany.
SOURCE: JOURNAL OF NEURAL TRANSMISSION. SUPPLEMENTUM, (1994) 43 145-62. Ref: 96
Journal code: 0425126. ISSN: 0303-6995.
PUB. COUNTRY: Austria
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199504
ENTRY DATE: Entered STN: 19950425
Last Updated on STN: 19960129
Entered Medline: 19950413

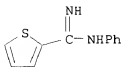
AB For several years there is controversy concerning the toxic potency of reaction products catalyzed by monoamine oxidase in neurodegenerative processes. There is uncertainty whether products of catecholamine oxidation are pathogenetically relevant factors for neuronal cell death in Parkinson's disease. To date products responsible for impairment of biochemical functions essential for cell viability are not yet identified, and the primary site of damage within the cell is unknown. Ammonia, aldehydes and hydrogen peroxide are formed via monoamine oxidase catalyzed oxidations of primary amines. But which of them, if any, is damaging to the cell? We discuss some aspects of the oxidative stress theory of cell degeneration in relation to toxicity of N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (**MPTP**) and to monoamine oxidation. Furthermore, we consider possible functional relationships of mitochondrial electron transfer reactions, toxicity of **MPTP** and MAO activity.

L22 ANSWER 40 OF 40 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 95123936 EMBASE
DOCUMENT NUMBER: 1995123936
TITLE: In vivo generation of hydroxyl radicals and **MPTP** -induced dopaminergic toxicity in the basal ganglia.
AUTHOR: Chiueh C.C.; Wu R.-M.; Mohanakumar K.P.; Sternberger L.M.; Krishna G.; Obata T.; Murphy D.L.
CORPORATE SOURCE: Unit Neurotoxicology Neuroprotection, Laboratory of Clinical Science, National Institutes of Health,Bethesda, MD 20892, United States
SOURCE: Annals of the New York Academy of Sciences, (1994) 738/- (25-36).
ISSN: 0077-8923 CODEN: ANYAA
COUNTRY: United States
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 008 Neurology and Neurosurgery
029 Clinical Biochemistry
LANGUAGE: English

Compound A searched in combination — no useful results - only HCl + HI

=> d l2 1-2

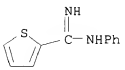
L2 ANSWER 1 OF 2 REGISTRY COPYRIGHT 2003 ACS
RN 59918-81-9 REGISTRY
CN 2-Thiophenecarboximidamide, N-phenyl-, monohydrochloride (9CI) (CA INDEX NAME)
MF C11 H10 N2 S . Cl H
LC STN Files: BEILSTEIN*, CA, CAPLUS, CASREACT
(*File contains numerically searchable property data)
CRN (3737-39-1)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

L2 ANSWER 2 OF 2 REGISTRY COPYRIGHT 2003 ACS
RN 59918-71-7 REGISTRY
CN 2-Thiophenecarboximidamide, N-phenyl-, monohydriodide (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 2-Thiophenecarboxamidine, N-phenyl-, hydriodide (7CI)
MF C11 H10 N2 S . H I
LC STN Files: BEILSTEIN*, CA, CAOLD, CAPLUS, CASREACT
(*File contains numerically searchable property data)
CRN (3737-39-1)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

2 REFERENCES IN FILE CA (1962 TO DATE)
2 REFERENCES IN FILE CAPLUS (1962 TO DATE)
1 REFERENCES IN FILE CAOLD (PRIOR TO 1967)